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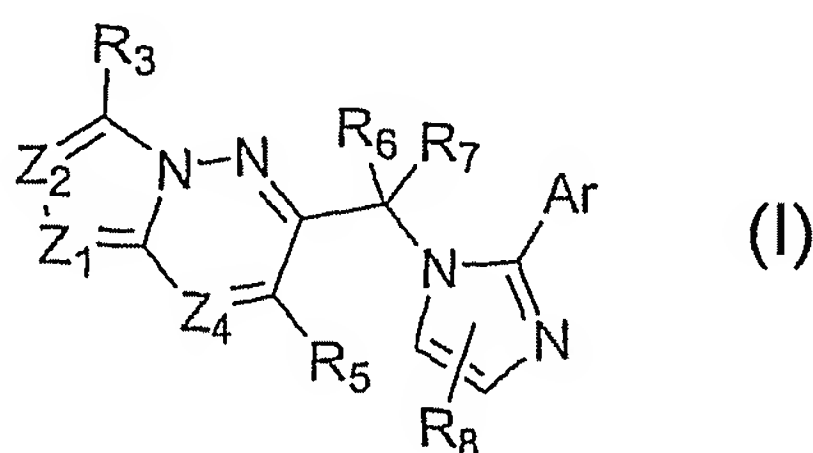
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(54) Title: IMIDAZO-PYRIDAZINES, TRIAZOLO-PYRIDAZINES AND RELATED BENZODIAZEPINE RECEPTOR LIG-
ANDS



(57) Abstract: Compounds of the Formula are provided, as are methods for their preparation. The variables Z₁, Z₂, R₃, Z₄, R₅, R₆, R₇, R₈ and Ar in the above formula are defined herein. Such compounds may be used to modulate ligand binding to GABA_A receptors in vivo or in vitro, and are particularly useful in the treatment of a variety of central nervous system (CNS) disorders in humans, domesticated companion animals and livestock animals. Compounds provided herein may be administered alone or in combination with one or more other CNS agents to potentiate the effects of the other CNS agent(s). Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for detecting GABA_A receptors (e.g., receptor localization studies).



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IMIDAZO-PYRIDAZINES, TRIAZOLO-PYRIDAZINES AND RELATED BENZODIAZEPINE RECEPTOR LIGANDS

5 FIELD OF THE INVENTION

The present invention relates generally to imidazopyridazines and triazolopyridazines that have useful pharmacological properties. The present invention further relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in the treatment of central nervous system (CNS) diseases.

10

BACKGROUND OF THE INVENTION

The GABA_A receptor superfamily represents one of the classes of receptors through which the major inhibitory neurotransmitter γ -aminobutyric acid (GABA) acts. Widely, although unequally, distributed throughout the mammalian brain, GABA mediates many of its actions through interaction with a complex of proteins called the GABA_A receptor, which causes alteration in chloride conductance and membrane polarization. A number of drugs, including the anxiolytic and sedating benzodiazepines, also bind to this receptor. The GABA_A receptor comprises a chloride channel that opens in response to GABA, allowing chloride to enter the cell. This, in turn, effects a slowing of neuronal activity through hyperpolarization of the cell membrane potential.

20 GABA_A receptors are composed of five protein subunits. A number of cDNAs for these GABA_A receptor subunits have been cloned and their primary structures determined. While these subunits share a basic motif of 4 membrane-spanning helices, there is sufficient sequence diversity to classify them into several groups. To date, at least six α , three β , three γ , one ϵ , one δ and two ρ subunits have been identified. Native GABA_A receptors are typically composed of two α subunits, two β subunits and one γ subunit. Various lines of evidence (such as message distribution, genome localization and biochemical study results) suggest that the major naturally occurring receptor combinations are $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$ and $\alpha_5\beta_3\gamma_2$.

30 The GABA_A receptor binding sites for GABA (two per receptor complex) are formed by amino acids from the α and β subunits. Amino acids from the α and γ subunits together form one benzodiazepine site per receptor, at which benzodiazepines exert their pharmacological activity. In addition, the GABA_A receptor contains sites of interaction for several other classes of drugs. These include a steroid binding site, a picrotoxin site and a barbiturate site. The benzodiazepine site of the GABA_A receptor is a distinct site on the receptor complex that does not overlap with the sites of interaction for other classes of drugs or GABA.

35 In a classic allosteric mechanism, the binding of a drug to the benzodiazepine site alters the affinity of the GABA receptor for GABA. Benzodiazepines and related drugs that enhance the ability of GABA to open GABA_A receptor channels are known as agonists or partial agonists, depending on

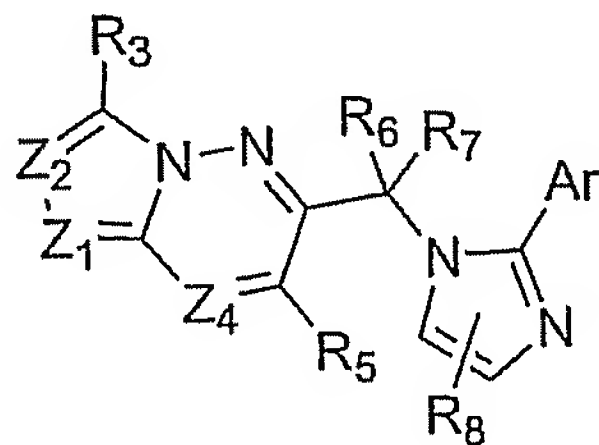
the level of GABA enhancement. Other classes of drugs, such as β -carboline derivatives, that occupy the same site and negatively modulate the action of GABA are called inverse agonists. Those compounds that occupy the same site, and yet have little or no effect on GABA activity, can block the action of agonists or inverse agonists and are thus referred to as GABA_A receptor antagonists.

5 The important allosteric effects of drugs acting at the benzodiazepine site were recognized early, and the distribution of activities at different receptor subtypes has been an area of intense pharmacological discovery. Agonists that act at the benzodiazepine site are known to exhibit anxiolytic, sedative, anticonvulsant and hypnotic effects, while compounds that act as inverse agonists at this site elicit anxiogenic, cognition enhancing and proconvulsant effects.

10 While benzodiazepines have enjoyed long pharmaceutical use, these compounds can exhibit a number of unwanted side effects. Accordingly, there is a need in the art for additional therapeutic agents that modulate GABA_A receptor activation and/or activity. The present invention fulfills this need, and provides further related advantages.

15 SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I:



Formula I

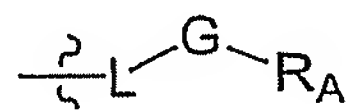
as well as pharmaceutically acceptable salts thereof, wherein:

Z₁ is nitrogen or CR₁ and Z₂ is nitrogen or CR₂, such that at least one of Z₁ and Z₂ is nitrogen;

20 Z₄ is nitrogen or CR₄;

R₁, R₂, R₃ and R₄ are each independently selected from:

- (a) hydrogen, halogen, nitro and cyano; and
- (b) groups of the formula:



25 wherein:

L is a single covalent bond or C₁-C₈alkylene;

G is a single covalent bond, N(R_B) (*i.e.*, $-\text{N}-$), O, C(=O) (*i.e.*, $-\text{C}-$), C(=O)O (*i.e.*, $-\text{C}-\text{O}-$),

C(=O)N(R_B) (*i.e.*, $-\text{C}-\text{N}-$), N(R_B)C(=O) (*i.e.*, $-\text{N}-\text{C}-$), S(O)_m (*i.e.*, $-\text{S}-$, $-\text{S}-$ or $-\text{S}-$),

$\text{CH}_2\text{C}(=\text{O})$ (*i.e.*, $\begin{array}{c} \text{H} \quad \text{O} \\ | \quad || \\ -\text{C}-\text{C}- \\ | \quad | \\ \text{H} \end{array}$), $\text{S}(\text{O})_m\text{N}(\text{R}_B)$ (*e.g.*, $\begin{array}{c} \text{O} \quad \text{O} \quad \text{R}_B \\ || \quad | \quad | \\ -\text{S}-\text{N}- \\ | \quad | \end{array}$) or $\text{N}(\text{R}_B)\text{S}(\text{O})_m$ (*e.g.*, $\begin{array}{c} \text{R}_B \quad \text{O} \quad \text{O} \\ | \quad || \quad | \\ -\text{N}-\text{S}- \\ | \quad | \end{array}$);
 wherein m is 0, 1 or 2; and

R_A and each R_B are independently selected from:

(i) hydrogen; and

- 5 (ii) C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, (C_3 - C_8 cycloalkyl) C_0 - C_4 alkyl, (3- to 6-membered heterocycloalkyl) C_0 - C_4 alkyl, (aryl) C_0 - C_2 alkyl and (heteroaryl) C_0 - C_2 alkyl, each of which is substituted with from 0 to 4 substituents independently selected from halogen, hydroxy, nitro, cyano, amino, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkanoyl, mono- and di(C_1 - C_4 alkyl)amino, C_1 - C_4 haloalkyl and C_1 - C_4 haloalkoxy;
- 10 R_5 is hydrogen, halogen, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_4 alkoxy, or mono- or di-(C_1 - C_4 alkyl)amino, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C_1 - C_4 alkoxy, C_1 - C_2 haloalkyl, C_1 - C_2 haloalkoxy, mono- and di- C_1 - C_4 alkylamino, C_3 - C_8 cycloalkyl, phenyl, phenyl C_1 - C_4 alkoxy and 5- or 6-membered heteroaryl;
- 15 R_6 and R_7 are independently hydrogen, methyl, ethyl or halogen;
- R_8 represents 0, 1 or 2 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, mono- and di(C_1 - C_4 alkyl)amino, C_3 - C_7 cycloalkyl, C_1 - C_2 haloalkyl and C_1 - C_2 haloalkoxy; and
- Ar represents phenyl, naphthyl or a 5- to 10-membered heteroaryl, each of which is substituted with
- 20 from 0 to 4 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C_1 - C_8 alkyl, C_1 - C_8 alkenyl, C_1 - C_8 alkynyl, C_1 - C_8 alkoxy, (C_3 - C_7 cycloalkyl) C_0 - C_4 alkyl, (C_3 - C_7 cycloalkyl) C_1 - C_4 alkoxy, C_2 - C_8 alkyl ether, C_3 - C_8 alkanone, C_1 - C_8 alkanoyl, 3- to 7-membered heterocycloalkyl, C_1 - C_8 haloalkyl, C_1 - C_8 haloalkoxy, oxo, C_1 - C_8 hydroxyalkyl, C_1 - C_8 aminoalkyl, and mono- and di-(C_1 - C_8 alkyl)amino C_0 - C_8 alkyl.

25 Within certain aspects, such compounds are GABA_A receptor modulators that modulate GABA_A receptor activation and/or GABA_A receptor-mediated signal transduction. Such GABA_A receptor modulators are preferably high affinity and/or high selectivity GABA_A receptor ligands and act as agonists, inverse agonists or antagonists of GABA_A receptors, such as human GABA_A receptors. As such, they are useful in the treatment of various CNS disorders.

30 Within further aspects, the present invention provides pharmaceutical compositions comprising one or more compounds or salts as described above in combination with a pharmaceutically acceptable carrier or excipient. Packaged pharmaceutical preparations are also provided, comprising such a pharmaceutical composition in a container and instructions for using the composition to treat a patient suffering from a CNS disorder such as anxiety, depression, a sleep disorder, attention deficit disorder,

35 schizophrenia, or a cognitive disorder such as short-term memory loss or Alzheimer's dementia.

The present invention further provides, within other aspects, methods for treating patients suffering from certain CNS disorders, such as anxiety, depression, a sleep disorder, attention deficit disorder, schizophrenia or a cognitive disorder, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound as described above. Methods for improving short term memory in a patient are also provided, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound as described above. Treatment of humans, domesticated companion animals (pets) or livestock animals suffering from certain CNS disorders with a compound as provided herein is encompassed by the present invention.

In a separate aspect, the invention provides methods of potentiating the action of other CNS active compounds. These methods comprise administering to a patient a therapeutically effective amount of a compound or salt of Formula I in conjunction with the administration of a therapeutically effective amount of another CNS active compound.

The present invention further relates to the use of compounds and salts of Formula I as probes for the localization of GABA_A receptors in sample (e.g., a tissue section). In certain embodiments, GABA_A receptors are detected using autoradiography. Additionally, the present invention provides methods for determining the presence or absence of GABA_A receptor in a sample, comprising the steps of: (a) contacting a sample with a compound as described above under conditions that permit binding of the compound to GABA_A receptor; (b) removing compound that is not bound to the GABA_A receptor and (c) detecting compound bound to GABA_A receptor.

In yet another aspect, the present invention provides methods for preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention provides compounds and salts of Formula I. Certain preferred compounds bind to GABA_A receptor, preferably with high selectivity; more preferably such compounds further provide beneficial modulation of brain function. Such compounds may be used *in vitro* or *in vivo* to determine the location of GABA_A receptors or to modulate GABA_A receptor activity in a variety of contexts.

CHEMICAL DESCRIPTION AND TERMINOLOGY

Compounds provided herein are generally described using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. All chiral (enantiomeric and diastereomeric) and racemic forms, as well as all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. Geometric isomers of olefins, C=N

double bonds and the like may also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers are also contemplated and may be isolated as a mixture of isomers or as separated isomeric forms. Compounds in which one or more atoms are replaced with an isotope (*i.e.*, an atom having the same atomic number but a different mass number) are also contemplated. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{11}C , ^{13}C and ^{14}C .

Certain general formulas recited herein include variables. Unless otherwise specified, each variable within such a formula is defined independently of other variables, and any variable that occurs more than one time within a formula is defined independently at each occurrence. Thus, for example, if a group is described as being substituted with 0-2 R^* , then the group may be unsubstituted or substituted with up to two R^* groups and R^* at each occurrence is selected independently from the definition of R^* . In addition, it will be apparent that combinations of substituents and/or variables are permissible only if such combinations result in a stable compound (*i.e.*, a compound that can be isolated, characterized and tested for biological activity).

A "pharmaceutically acceptable salt" is an acid or base salt form of a compound, which salt form is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanoic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985). In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile, is preferred.

It will be apparent that each compound of Formula I may, but need not, be formulated as a hydrate, solvate or non-covalent complex. In addition, the various crystal forms and polymorphs are

within the scope of the present invention. Also provided herein are prodrugs of the compounds of Formula I. A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound of Formula I, or other formula provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to yield the parent compounds.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other substituent discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated substituents, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound (*i.e.*, a compound that can be isolated, characterized and tested for biological activity). When a substituent is oxo (*i.e.*, =O), then 2 hydrogens on the atom are replaced. When aromatic moieties are substituted by an oxo group, the aromatic ring is replaced by the corresponding partially unsaturated ring. For example a pyridyl group substituted by oxo is a pyridone.

The phrase "optionally substituted" indicates that a group may either be unsubstituted or substituted at one or more of any of the available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable substituents such as those disclosed herein. Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," in which X is the maximum number of substituents.

A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups; where specified, such a group has the indicated number of carbon atoms. Thus, the term C₁-C₆alkyl, as used herein, indicates an alkyl group having from 1 to 6 carbon atoms. "C₀-C₄alkyl" refers to a single covalent bond or a C₁-C₄alkyl group. Alkyl groups include groups having from 1 to 8 carbon atoms (C₁-C₈alkyl), from 1 to 6 carbon atoms (C₁-C₆alkyl) and from 1 to 4 carbon atoms (C₁-C₄alkyl), such as methyl, ethyl, n-propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. In certain embodiments, preferred alkyl groups are methyl, ethyl, propyl, butyl and 3-pentyl. "Aminoalkyl" is an alkyl group as defined herein substituted with one or more -NH₂ substituents. "Hydroxyalkyl" is an

alkyl group as defined herein substituted with one or more -OH substituents. The term "alkylene" refers to a divalent alkyl group.

"Alkenyl" refers to a straight or branched hydrocarbon chain comprising one or more carbon-carbon double bonds, such as ethenyl and propenyl. Alkenyl groups include C₂-C₈alkenyl, C₂-C₆alkenyl and C₂-C₄alkenyl groups (which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively), such as ethenyl, allyl or isopropenyl.

"Alkynyl" refers to straight or branched hydrocarbon chains comprising one or more carbon-carbon triple bonds. Alkynyl groups include C₂-C₈alkynyl, C₂-C₆alkynyl and C₂-C₄alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively. Alkynyl groups include for example groups such as ethynyl and propynyl.

By "alkoxy," as used herein, is meant an alkyl group as described above attached via an oxygen bridge. Alkoxy groups include C₁-C₆alkoxy and C₁-C₄alkoxy groups, which have from 1 to 6 or 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy and 3-methylpentoxy are specific alkoxy groups.

A "cycloalkyl" is a saturated or partially saturated cyclic group in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of any of the foregoing, such as cyclohexenyl. Such groups typically contain from 3 to about 10 ring carbon atoms; in certain embodiments, such groups have from 3 to 7 ring carbon atoms (*i.e.*, C₃-C₇cycloalkyl). If substituted, any ring carbon atom may be bonded to any indicated substituent.

In the term "(cycloalkyl)alkyl," "cycloalkyl" and "alkyl" are as defined above, and the point of attachment is on the alkyl group. Certain such groups are (C₃-C₈cycloalkyl)C₀-C₄alkyl, in which the cycloalkyl group is linked via a single covalent bond or a C₁-C₄alkyl. This term encompasses, for example, cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl. Similarly, "(C₃-C₇cycloalkyl)C₁-C₄alkoxy" refers to a C₃-C₇cycloalkyl group linked via a C₁-C₄alkoxy.

The term "alkanoyl" refers to an alkyl group as defined above attached through a carbonyl bridge. Alkanoyl groups include C₁-C₈alkanoyl, C₁-C₄alkanoyl and C₂-C₄alkanoyl groups, which have from 1 to 8, 1 to 4 or 2 to 4 carbon atoms, respectively. "C₁alkanoyl" refers to -(C=O)-H. Ethanoyl is C₂alkanoyl.

The term "oxo," as used herein, refers to a keto (C=O) group. An oxo group that is a substituent of a nonaromatic ring results in a conversion of -CH₂- to -C(=O)-. It will be apparent that the introduction of an oxo substituent on an aromatic ring destroys the aromaticity.

An "alkanone" is an alkyl group as defined above with the indicated number of carbon atoms substituted at a non-terminal position with an oxo group. "C₃-C₈alkanone," "C₃-C₆alkanone" and "C₃-

C₄alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C₃ alkanone group has the structure $-\text{CH}_2-(\text{C}=\text{O})-\text{CH}_3$.

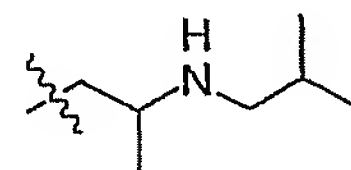
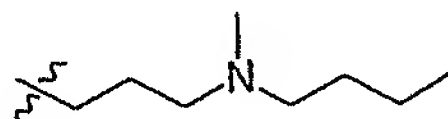
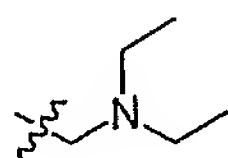
Similarly, "alkyl ether" refers to a linear or branched ether substituent linked via a carbon-carbon bond. Alkyl ether groups include C₂-C₈alkyl ether, C₂-C₆alkyl ether and C₂-C₄alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C₂ alkyl ether group has the structure $-\text{CH}_2-\text{O}-\text{CH}_3$.

The term "alkoxycarbonyl" refers to an alkoxy group linked via a carbonyl (*i.e.*, a group having the general structure $-\text{C}(=\text{O})-\text{O}-\text{alkyl}$). Alkoxycarbonyl groups include C₁-C₆ and C₁-C₄alkoxycarbonyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively.

"C₁alkoxycarbonyl" refers to $-\text{C}(=\text{O})-\text{OH}$.

The term "aminocarbonyl" refers to an amide group (*i.e.*, $-(\text{C}=\text{O})\text{NH}_2$).

"Alkylamino" refers to a secondary or tertiary amine substituent having the general structure $-\text{NH}-\text{alkyl}$ or $-\text{N}(\text{alkyl})(\text{alkyl})$, wherein each alkyl may be the same or different. Such groups include, for example, mono- and di-(C₁-C₄alkyl)amino groups, in which each alkyl may be the same or different and may contain from 1 to 4 carbon atoms. Alkylaminoalkyl refers to an alkylamino group linked via an alkyl group (*i.e.*, a group having the general structure $-\text{alkyl}-\text{NH}-\text{alkyl}$ or $-\text{alkyl}-\text{N}(\text{alkyl})(\text{alkyl})$). Such groups include, for example, mono- and di-(C₁-C₈alkyl)aminoC₁-C₈alkyl, in which each alkyl may be the same or different. "Mono- or di-(C₁-C₈alkyl)aminoC₀-C₈alkyl" refers to a mono- or di-(C₁-C₈alkyl)amino group linked via a single covalent bond or a C₁-C₈alkyl group. The following are representative alkylaminoalkyl groups:



The term "halogen" refers to fluorine, chlorine, bromine and iodine. A "haloalkyl" is a branched or straight-chain alkyl group, substituted with 1 or more halogen atoms (*e.g.*, "C₁-C₈haloalkyl" groups have from 1 to 8 carbon atoms; "C₁-C₂haloalkyl" groups have from 1 to 2 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; and mono-, di-, tri-, tetra- or penta-chloroethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "C₁-C₈haloalkoxy" groups have from 1 to 8 carbon atoms.

As used herein, the term "aryl" indicates aromatic groups containing only carbon in the aromatic ring(s). Such aromatic groups may be further substituted with carbon or non-carbon atoms or groups. Typical aryl groups contain from 1 to 3 separate, fused, spiro or pendant rings and from 6 to about 18 ring atoms, without heteroatoms as ring members. Preferred aryl groups are 6- to 12-membered groups, such as phenyl, naphthyl (including 1-naphthyl and 2-naphthyl) and biphenyl. Arylalkyl groups are aryl groups linked via an alkyl group; arylalkoxy groups are aryl groups linked via

an alkoxy moiety. "(Aryl)C₀-C₂alkyl" refers to an aryl group linked via a single covalent bond or via a methylene or ethylene group. PhenylC₁-C₄alkoxy refers to a C₁-C₄alkoxy group with a phenyl substituent.

The term "heterocycle" or "heterocyclic group" is used to indicate saturated, partially unsaturated or aromatic groups having 1 or 2 rings, with 3 to 8 atoms in each ring, and in at least one ring from 1 to 4 independently chosen heteroatoms (*i.e.*, oxygen, sulfur or nitrogen). The heterocyclic ring may be attached via any ring heteroatom or carbon atom that results in a stable structure, and may be substituted on carbon and/or nitrogen atom(s) if the resulting compound is stable. Any nitrogen and/or sulfur heteroatoms may optionally be oxidized, and any nitrogen may optionally be quaternized.

Certain heterocycles are "heteroaryl" (*i.e.*, comprise at least one aromatic ring having from 1 to 4 heteroatoms, with the remaining ring atoms being carbon), such as 5- to 7-membered monocyclic groups and 7- to 10-membered bicyclic groups. When the total number of S and O atoms in the heteroaryl group exceeds 1, then these heteroatoms are not adjacent to one another; preferably the total number of S and O atoms in the heteroaryl group is not more than 1, 2 or 3, more preferably not more than 1 or 2 and most preferably not more than 1. Examples of heteroaryl groups include pyridyl, indolyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, oxazolyl, thienyl, thiazolyl, triazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl and 5,6,7,8-tetrahydroisoquinoline. Bicyclic heteroaryl groups may, but need not, contain a saturated ring in addition to the aromatic ring (*e.g.*, a tetrahydroquinolinyl or tetrahydroisoquinolinyl group). A "5- or 6-membered heteroaryl" is a monocyclic heteroaryl having 5 or 6 ring members.

Other heterocycles are referred to herein as "heterocycloalkyl" (*i.e.*, saturated or partially saturated heterocycles). Heterocycloalkyl groups have from 3 to about 8 ring atoms, and more typically from 3 to 7 (or from 5 to 7) ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl and pyrrolidinyl. A (3- to 6-membered heterocycloalkyl)C₀-C₄alkyl group is a heterocycloalkyl group having from 3 to 6 ring members that is linked via a single covalent bond or a C₁-C₄alkyl group. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl and pyrrolidinyl groups.

The terms "GABA_A receptor" and "benzodiazepine receptor" refer to a protein complex that detectably binds GABA and mediates a dose dependent alteration in chloride conductance and membrane polarization. Receptors comprising naturally-occurring mammalian (especially human or rat) GABA_A receptor subunits are generally preferred, although subunits may be modified provided that any modifications do not substantially inhibit the receptor's ability to bind GABA (*i.e.*, at least 50% of the binding affinity of the receptor for GABA is retained). The binding affinity of a candidate GABA_A receptor for GABA may be evaluated using a standard ligand binding assay as provided herein. It will be apparent that there are a variety of GABA_A receptor subtypes that fall within the scope of the term "GABA_A receptor." These subtypes include, but are not limited to, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, $\alpha_5\beta_3\gamma_2$ and $\alpha_1\beta_2\gamma_2$ receptor subtypes. GABA_A receptors may be obtained from a variety of sources, such as from

preparations of rat cortex or from cells expressing cloned human GABA_A receptors. Particular subtypes may be readily prepared using standard techniques (*e.g.*, by introducing mRNA encoding the desired subunits into a host cell, as described herein).

5 An "agonist" of a GABA_A receptor is a compound that enhances the activity of GABA at the GABA_A receptor. Agonists may, but need not, also enhance the binding of GABA to GABA_A receptor. The ability of a compound to act as a GABA_A agonist may be determined using an electrophysiological assay, such as the assay provided in Example 5.

10 An "inverse agonist" of a GABA_A receptor is a compound that reduces the activity of GABA at the GABA_A receptor. Inverse agonists, but need not, may also inhibit binding of GABA to the GABA_A receptor. The reduction of GABA-induced GABA_A receptor activity may be determined from an electrophysiological assay such as the assay of Example 5.

15 An "antagonist" of a GABA_A receptor, as used herein, is a compound that occupies the benzodiazepine site of the GABA_A receptor, but has no detectable effect on GABA activity at the GABA_A receptor. Such compounds can inhibit the action of agonists or inverse agonists. GABA_A receptor antagonist activity may be determined using a combination of a suitable GABA_A receptor binding assay, such as the assay provided in Example 4, and a suitable functional assay, such as the electrophysiological assay provided in Example 5, herein.

20 A "GABA_A receptor modulator" is any compound that acts as a GABA_A receptor agonist, inverse agonist or antagonist. In certain embodiments, such a modulator may exhibit an affinity constant (K_i) of less than 1 micromolar in a standard GABA_A receptor radioligand binding assay, or an EC_{50} of less than 1 micromolar in an electrophysiological assay. In other embodiments a GABA_A receptor modulator may exhibit an affinity constant or EC_{50} of less than 500 nM, 200 nM, 100 nM, 50 nM, 25 nM, 10 nM or 5 nM.

25 A GABA_A receptor modulator is said to have "high affinity" if the K_i at a GABA_A receptor is less than 1 micromolar, preferably less than 100 nanomolar or less than 10 nanomolar. A representative assay for determining K_i at GABA_A receptor is provided in Example 4, herein. It will be apparent that the K_i may depend upon the receptor subtype used in the assay. In other words, a high affinity compound may be "subtype-specific" (*i.e.*, the K_i is at least 10-fold greater for one subtype than for another subtype). Such compounds are said to have high affinity for GABA_A receptor if the K_i for at least one GABA_A receptor subtype meets any of the above criteria.

30 A GABA_A receptor modulator is said to have "high selectivity" if it binds to at least one subtype of GABA_A receptor with a K_i that is at least 10-fold lower, preferably at least 100-fold lower, than the K_i for binding to other (*i.e.*, not GABA_A) membrane-bound receptors. In particular, a compound that displays high selectivity should have a K_i that is at least 10-fold greater at the following receptors than at a GABA_A receptor: serotonin, dopamine, galanin, VR1, C5a, MCH, NPY, CRF, bradykinin and tachykinin. Assays to determine K_i at other receptors may be performed using standard binding assay protocols, such as using a commercially available membrane receptor binding assay (*e.g.*,

the binding assays available from MDS PHARMA SERVICES, Toronto, Canada and CEREP, Redmond, WA).

A "CNS disorder" is a disease or condition of the central nervous system that is responsive to GABA_A receptor modulation in the patient. Such disorders include anxiety disorders (*e.g.*, panic disorder, obsessive compulsive disorder, agoraphobia, social phobia, specific phobia, dysthymia, adjustment disorders, separation anxiety, cyclothymia and generalized anxiety disorder), stress disorders (*e.g.*, post-traumatic stress disorder, anticipatory anxiety acute stress disorder and acute stress disorder), depressive disorders (*e.g.*, depression, atypical depression, bipolar disorder and depressed phase of bipolar disorder), sleep disorders (*e.g.*, primary insomnia, circadian rhythm sleep disorder, dyssomnia NOS, parasomnias including nightmare disorder, sleep terror disorder, sleep disorders secondary to depression, anxiety and/or other mental disorders and substance-induced sleep disorder), cognitive disorders (*e.g.*, cognition impairment, mild cognitive impairment (MCI), age-related cognitive decline (ARCD), schizophrenia, traumatic brain injury, Down's Syndrome, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease and stroke), AIDS-associated dementia, dementia associated with depression, anxiety or psychosis, attention deficit disorders (*e.g.*, attention deficit disorder and attention deficit and hyperactivity disorder), convulsive disorders (*e.g.*, epilepsy), benzodiazepine overdose and drug and alcohol addiction.

A "CNS agent" is any drug used to treat or prevent a CNS disorder or to induce or prolong sleep in a healthy patient. CNS agents include, for example: GABA_A receptor modulators, serotonin receptor (*e.g.*, 5-HT_{1A}) agonists and antagonists and selective serotonin reuptake inhibitors (SSRIs); neurokinin receptor antagonists; corticotropin releasing factor receptor (CRF₁) antagonists; melatonin receptor agonists; nicotinic agonists; muscarinic agents; acetylcholinesterase inhibitors and dopamine receptor agonists.

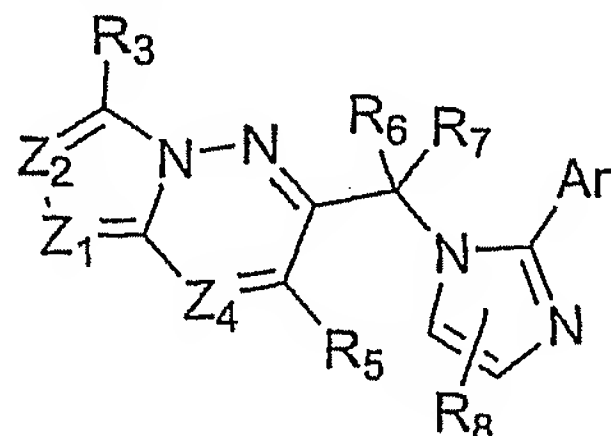
A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (*e.g.*, diminution of one or more symptoms of a CNS disorder or promotion of a desired effect on sleep). Such an amount or dose generally results in a concentration of compound in cerebrospinal fluid that is sufficient to inhibit the binding of GABA_A receptor ligand to GABA_A receptor *in vitro*, as determined using the assay described in Example 4. It will be apparent that the therapeutically effective amount for a compound will depend upon the indication for which the compound is administered, as well as any co-administration of other CNS agent(s). It will be apparent that the discernible patient benefit may be apparent after administration of a single dose, or may become apparent following repeated administration of the therapeutically effective dose according to a prescribed regimen, depending upon the indication for which the compound is administered.

A "patient" is any individual treated with a compound provided herein. Patients include humans, as well as other vertebrate animals such as companion animals and livestock. Patients may be

afflicted with a CNS disorder, or may be free of such a condition (*i.e.*, treatment may be prophylactic or soporific).

IMIDAZOPYRIDAZINES AND TRIAZOLOPYRIDAZINES

As noted above, the present invention provides compounds of Formula I, with the variables as described above, and pharmaceutically acceptable salts of such compounds.



Formula I

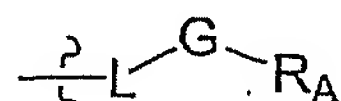
In certain compounds provided herein, R₈ represents 0 substituents or 1 substituent selected from halogen, C₁-C₂alkyl and C₁-C₂alkoxy.

Ar, within certain compounds of Formula I, is substituted with 0, 1, 2 or 3 substituents independently selected from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy, mono- and di-(C₁-C₄alkyl)amino, C₂-C₄alkanoyl, (C₃-C₇cycloalkyl)C₀-C₂alkyl, C₁-C₂haloalkyl and C₁-C₂haloalkoxy.

In certain embodiments, Ar is phenyl, pyridyl, thiazolyl, thienyl, pyridazinyl or pyrimidinyl, each of which is substituted with from 0 to 4 substituents as described above, or substituted with from 0 to 3 substituents independently selected from chloro, fluoro, hydroxy, cyano, amino, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₂alkylamino, C₁-C₂haloalkyl and C₁-C₂haloalkoxy. Representative Ar groups include phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl and pyridazin-3-yl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C₁-C₂alkyl, cyano and C₁-C₂alkoxy. For example, Ar groups include, but are not limited to, 2,6-difluoro-phenyl, 2,5-difluoro-phenyl, 5-fluoro-2-methyl-phenyl, pyridin-2-yl, 3-fluoro-pyridin-2-yl, 3-cyano-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 3-hydroxy-pyridin-2-yl, 3-methoxy-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 6-cyano-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, 6-hydroxy-pyridin-2-yl and 6-methoxy-pyridin-2-yl.

R₁, R₂, R₃ and R₄, in certain compounds, are independently selected from:

- (a) hydrogen, halogen and cyano; and
- (b) groups of the formula:



wherein:

- (i) L is a single covalent bond;
- (ii) G is a single covalent bond, NH, N(R_B), O, C(=O)O or C(=O); and
- (iii) R_A and R_B are independently selected from (1) hydrogen and (2) C₁-C₆alkyl, C₂-C₆alkenyl, (C₃-C₇cycloalkyl)C₀-C₂alkyl, phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl and pyrazinyl,

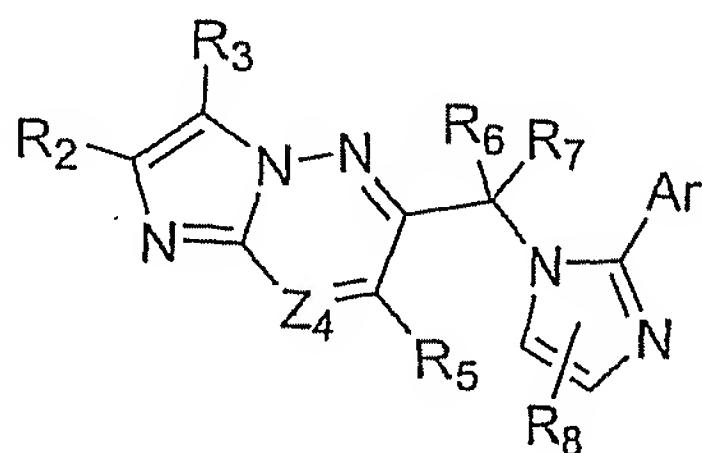
each of which is substituted with from 0 to 4 substituents independently selected from hydroxy, halogen, cyano, amino, C₁-C₂alkyl and C₁-C₂alkoxy.

For example, R₁, R₂, R₃ and R₄ are independently selected, in certain compounds, from hydrogen, hydroxy, halogen, cyano, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₃-C₇cycloalkyl, C₁-C₄hydroxyalkyl, C₁-C₂haloalkyl, C₁-C₂haloalkoxy, C₁-C₆alkoxycarbonyl, mono- and di-(C₁-C₄alkyl)amino, phenyl and pyridyl. Representative R₃ and R₄ groups include hydrogen, methyl and ethyl. In certain embodiments, Z₁ is nitrogen and Z₂ is CR₂. Representative R₂ groups include hydrogen, cyano, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₂-C₄alkyl ether, C₃-C₇cycloalkyl, C₁-C₂hydroxyalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl and pyridyl. In other embodiments, Z₁ is CR₁ and Z₂ is nitrogen. Representative R₂ groups include hydrogen, cyano, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₂-C₄alkyl ether, C₃-C₇cycloalkyl, C₁-C₂hydroxyalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl and pyridyl. In further embodiments, Z₁ and Z₂ are nitrogen.

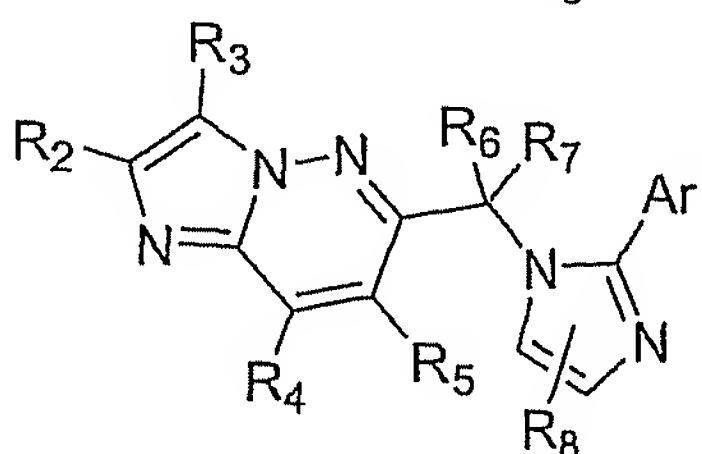
In certain compounds of Formula I, R₅ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy, or mono- or di-C₁-C₄alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C₁-C₂alkoxy, C₃-C₈cycloalkyl, phenyl and phenylC₁-C₂alkoxy. Representative R₅ groups include ethyl, propyl, butyl, ethoxy and methoxymethyl.

R₆ and R₇, within certain embodiments, are both hydrogen.

Certain compounds of Formula I further satisfy Formula II (in which Z₁ is nitrogen and Z₂ is CR₂) or Formula IIa (in which Z₁ is nitrogen, Z₂ is CR₂ and Z₄ is CR₄):



Formula II



Formula IIa

In certain such compounds,

R₂ is selected from hydrogen, hydroxy, halogen, cyano, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₇cycloalkyl, C₂-C₆alkyl ether, C₁-C₄hydroxyalkyl, C₁-C₂haloalkyl, C₁-C₂haloalkoxy, C₁-C₄alkoxycarbonyl, mono- and di-(C₁-C₄alkyl)amino, phenyl and pyridyl;

R₃ and R₄ are independently hydrogen or C₁-C₄alkyl;

R₅ is C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₄alkoxy, or mono- or di-C₁-C₄alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C₁-C₂alkoxy, C₃-C₈cycloalkyl, phenyl and phenylC₁-C₂alkoxy;

R_6 and R_7 are independently hydrogen, methyl, ethyl or halogen;

R_8 represents 0 or 1 substituent selected from halogen, C_1 - C_2 alkyl and C_1 - C_2 alkoxy; and

Ar represents phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl or 3-pyridazinyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, cyano and C_1 - C_2 alkoxy.

In further such compounds:

R_2 is hydrogen, cyano, aminocarbonyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_2 - C_6 alkyl ether, C_1 - C_4 hydroxyalkyl, C_1 - C_2 haloalkyl or C_1 - C_4 alkoxycarbonyl;

R_3 and R_4 are independently hydrogen or C_1 - C_2 alkyl;

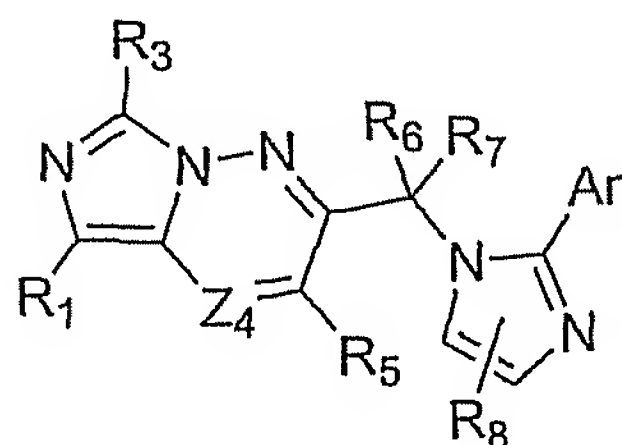
R_5 is C_1 - C_6 alkyl or C_2 - C_6 alkenyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy and C_1 - C_2 alkoxy;

R_6 and R_7 are hydrogen;

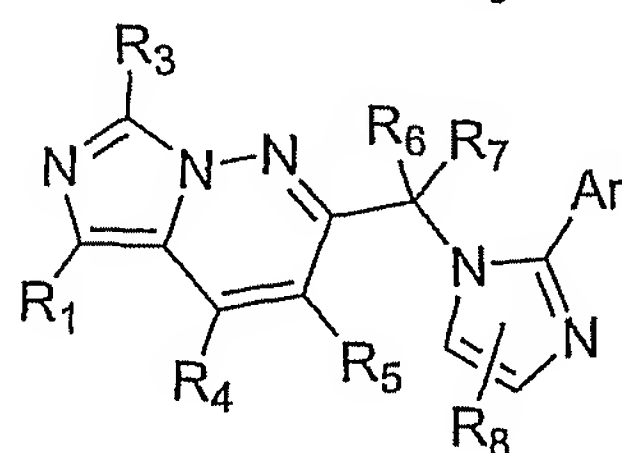
R_8 represents 0 substituents; and

Ar represents phenyl or 2-pyridyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, cyano and C_1 - C_2 alkoxy.

Certain compounds of Formula I further satisfy Formula III (in which Z_1 is CR_1 and Z_2 is N) or Formula IIIa (in which Z_1 is CR_1 , Z_2 is N and Z_4 is CR_4):



Formula III



Formula IIIa

In certain such compounds:

R_1 is selected from hydrogen, hydroxy, halogen, cyano, aminocarbonyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkyl, C_2 - C_6 alkyl ether, C_1 - C_4 hydroxyalkyl, C_1 - C_2 haloalkyl, C_1 - C_2 haloalkoxy, C_1 - C_4 alkoxycarbonyl, mono- and di- $(C_1$ - C_4 alkyl)amino, phenyl and pyridyl;

R_3 and R_4 are independently hydrogen or C_1 - C_4 alkyl;

R_5 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_4 alkoxy, or mono- or di- C_1 - C_4 alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C_1 -

C_2 alkoxy, C_3 - C_8 cycloalkyl, phenyl and phenyl C_1 - C_2 alkoxy;

R_6 and R_7 are independently hydrogen, methyl, ethyl or halogen;

R_8 represents 0 or 1 substituent selected from halogen, C_1 - C_2 alkyl and C_1 - C_2 alkoxy; and

Ar represents phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl or 3-pyridazinyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

In further such compounds:

5 R₁ is hydrogen, cyano, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₂-C₆alkyl ether, C₁-C₄hydroxyalkyl, C₁-C₂haloalkyl or C₁-C₄alkoxycarbonyl;

R₃ and R₄ are independently hydrogen or C₁-C₂alkyl;

R₅ is C₁-C₆alkyl or C₂-C₆alkenyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy and C₁-C₂alkoxy;

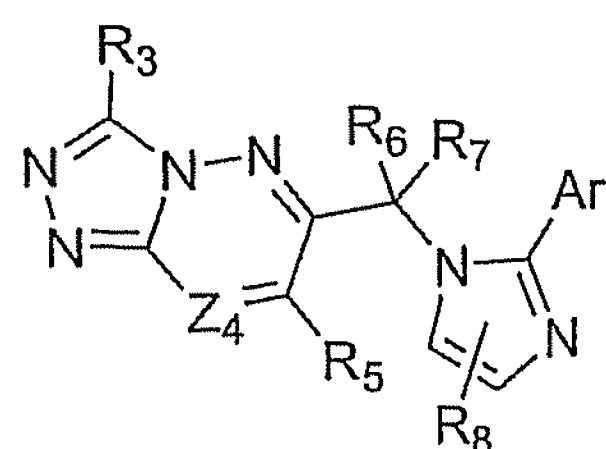
10 R₆ and R₇ are hydrogen;

R₈ represents 0 substituents; and

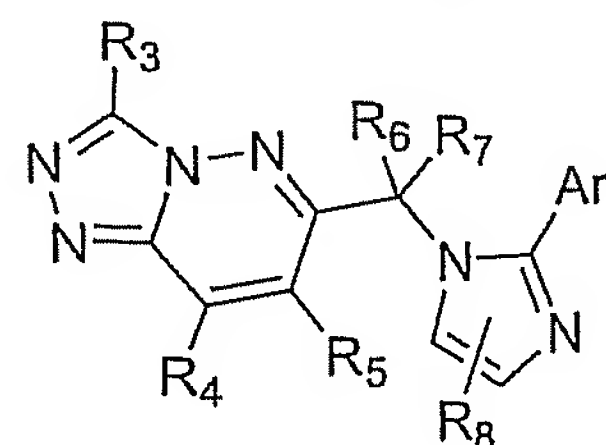
Ar represents phenyl or 2-pyridyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

Certain compounds of Formula I further satisfy Formula IV (in which Z₁ and Z₂ are nitrogen)

15 or Formula IVa (in which Z₁ and Z₂ are nitrogen and Z₄ is CR₄):



Formula IV



Formula IVa

In certain such compounds:

R₃ and R₄ are independently hydrogen or C₁-C₄alkyl;

R₅ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy, or mono- or di-C₁-C₄alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C₁-

20 C₂alkoxy, C₃-C₈cycloalkyl, phenyl and phenylC₁-C₂alkoxy;

R₆ and R₇ are independently hydrogen, methyl, ethyl or halogen;

R₈ represents 0 or 1 substituent selected from halogen, C₁-C₂alkyl and C₁-C₂alkoxy; and

Ar represents phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl or 3-pyridazinyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C₁-

25 C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

In further such compounds:

R₃ and R₄ are independently hydrogen or C₁-C₂alkyl;

R₅ is C₁-C₆alkyl or C₂-C₆alkenyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy and C₁-C₂alkoxy;

R₆ and R₇ are hydrogen;

R₈ represents 0 substituents; and

- 5 Ar represents phenyl or 2-pyridyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

In certain aspects, compounds provided herein detectably alter (modulate) ligand binding to GABA_A receptor, as determined using a standard *in vitro* receptor binding assay. References herein to a "GABA_A receptor ligand binding assay" are intended to refer to the standard *in vitro* receptor binding
10 assay provided in Example 4. Briefly, a competition assay may be performed in which a GABA_A receptor preparation is incubated with labeled (*e.g.*, ³H) ligand, such as Flumazenil, and unlabeled test compound. Incubation with a compound that detectably modulates ligand binding to GABA_A receptor will result in a decrease or increase in the amount of label bound to the GABA_A receptor preparation, relative to the amount of label bound in the absence of the compound. Preferably, such a compound
15 will exhibit a K_i at GABA_A receptor of less than 1 micromolar, more preferably less than 500 nM, 100 nM, 20 nM or 10 nM. The GABA_A receptor used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of rat cortex or from cells expressing cloned human GABA_A receptors.

In certain embodiments, preferred compounds provided herein have favorable pharmacological
20 properties, including oral bioavailability (such that a sub-lethal or preferably a pharmaceutically acceptable oral dose, preferably less than 2 grams, more preferably less than or equal to one gram or 200 mg, can provide a detectable *in vivo* effect), low toxicity (a preferred compound is nontoxic when a therapeutically effective amount is administered to a subject), minimal side effects (a preferred compound produces side effects comparable to placebo when a therapeutically effective amount of the
25 compound is administered to a subject), low serum protein binding, and a suitable *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing and most preferably once-a-day dosing). Distribution in the body to sites of target receptor activity is also desirable (*e.g.*, compounds used to treat CNS disorders will preferably penetrate the blood brain barrier, while low brain levels of compounds used to
30 treat peripheral disorders are typically preferred).

Routine assays that are well known in the art may be used to assess these properties and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, such as Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the
35 compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays, such as those described by Oravcová, et al. (1996) *Journal of Chromatography B* 677:1-27. Compound half-life is inversely proportional to the required frequency

of dosage. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (1998) *Drug Metabolism and Disposition* 26:1120-27.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria when administered at a minimum therapeutically effective amount or when contacted with cells at a concentration that is sufficient to inhibit the binding of GABA_A receptor ligand to GABA_A receptor *in vitro*: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement or (4) does not cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that, when tested as described in Example 10, does not decrease cellular ATP levels by more than 50%. Preferably, cells treated as described in Example 10 exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells. Highly preferred compounds are those that do not substantially inhibit cellular ATP production when the concentration of compound is at least 10-fold, 100-fold or 1000-fold greater than the EC₅₀ or IC₅₀ for the compound.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that yields a serum concentration equal to the EC₅₀ or IC₅₀ for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the p<0.1 level or more preferably at the p<0.05 level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC₅₀ or IC₅₀ for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound does not promote substantial release of liver enzymes if administration of a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 3-fold (preferably no more than 2-fold) over matched mock-treated controls. In more highly preferred embodiments, such doses do not
5 elevate such serum levels by more than 75% or 50% over matched controls. Alternately, a compound does not promote substantial release of liver enzymes if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) concentrations that are equal to the EC_{50} or IC_{50} for the compound do not cause detectable release of
10 any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are two-fold, five-fold, and preferably ten-fold the EC_{50} or IC_{50} for the compound.

In other embodiments, certain preferred compounds do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity,
15 CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC_{50} or IC_{50} for the compound.

Certain preferred compounds are not clastogenic or mutagenic (*e.g.*, as determined using standard assays such as the Chinese hamster ovary cell *vitro* micronucleus assay, the mouse lymphoma assay, the human lymphocyte chromosomal aberration assay, the rodent bone marrow micronucleus
20 assay, the Ames test or the like) at a concentration equal to the EC_{50} or IC_{50} for the compound. In other embodiments, certain preferred compounds do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, compounds provided herein may be isotopically-labeled or radiolabeled. Such compounds are identical to those described above, but for
25 the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as 2H , 3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy isotopes such as deuterium (*i.e.*, 2H) can afford certain
30 therapeutic advantages resulting from greater metabolic stability, such as increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

As noted above, different stereoisomeric forms, such as racemates and optically active forms, are encompassed by the present invention. In certain embodiments, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include
35 asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example, a chiral HPLC column.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising at least one GABA_A receptor modulator provided herein, together with at least one physiologically acceptable carrier or excipient. Such compounds may be used for treating patients in which GABA_A receptor modulation is desirable (*e.g.*, patients undergoing painful procedures who would benefit from the induction of amnesia, or those suffering from anxiety, depression, sleep disorders or cognitive impairment). Pharmaceutical compositions may comprise, for example, water, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. Preferred pharmaceutical compositions are formulated for oral delivery to humans or other animals (*e.g.*, companion animals such as dogs or cats). If desired, other active ingredients may also be included, such as additional CNS-active agents.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions in a form suitable for oral use are preferred. Such forms include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions comprise the active materials in admixture with one or more excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and/or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. One or more sweetening agents and/or flavoring agents may be added to provide palatable oral preparations. Such suspension may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil) or a mineral oil (*e.g.*, liquid paraffin) or mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*, sorbitan monooleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monooleate). The emulsions may also contain sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The compound, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution

and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Pharmaceutical compositions may also be prepared in the form of suppositories (e.g., for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

For administration to non-human animals, the composition may also be added to animal feed or drinking water. It may be convenient to formulate animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Pharmaceutical compositions may be formulated as sustained release formulations (i.e., a formulation such as a capsule that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active compound release. The amount of compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Compounds provided herein are generally present within a pharmaceutical composition in a therapeutically effective amount, as described above. Compositions providing dosage levels ranging from about 0.1 mg to about 140 mg per kilogram of body weight per day are preferred (about 0.5 mg to about 7 g per human patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient. It will be understood, however, that the optimal dose for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time and route of administration; the rate of excretion; any simultaneous treatment, such as a drug combination; and the type and severity of the particular disease undergoing treatment. Optimal dosages may be established using routine testing and procedures that are well known in the art.

Pharmaceutical compositions may be packaged for treating a CNS disorder such as anxiety, depression, a sleep disorder, attention deficit disorder or a cognitive disorder such as short-term memory loss or Alzheimer's dementia. Packaged pharmaceutical preparations include a container

METHODS OF USE

Frequency of dosage may vary, depending on the compound used and the particular disease to be treated or prevented. In general, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For soporific treatment, a single dose that rapidly reaches a concentration in cerebrospinal fluid that is sufficient to inhibit the binding of GABA_A receptor ligand to GABA_A receptor *in vitro* is desirable. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art.

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receptor subtype are useful in treating sleep disorders and convulsive disorders such as epilepsy. Compounds that act as antagonists at the benzodiazepine site are useful in reversing the effect of benzodiazepine overdose and in treating drug and alcohol addiction.

CNS disorders that can be treated using compounds and compositions provided herein include:

5 Depression, e.g., major depression, dysthymic disorder, atypical depression, bipolar disorder and depressed phase of bipolar disorder.

Anxiety, e.g., general anxiety disorder (GAD), agoraphobia, panic disorder +/- agoraphobia, social phobia, specific phobia, post traumatic stress disorder, obsessive compulsive disorder (OCD), dysthymia, adjustment disorders with disturbance of mood and anxiety, separation anxiety disorder, 10 anticipatory anxiety acute stress disorder, adjustment disorders and cyclothymia.

Sleep disorders, e.g., primary insomnia, circadian rhythm sleep disorder, dyssomnia NOS, parasomnias, including nightmare disorder, sleep terror disorder, sleep disorders secondary to depression and/or anxiety or other mental disorders, and substance induced sleep disorder. Representative treatable symptoms of sleep disorders include, for example, difficulty falling asleep, 15 excessive waking during the night, waking too early and waking feeling unrefreshed.

Cognition Impairment, e.g., Alzheimer's disease, Parkinson's disease, mild cognitive impairment (MCI), age-related cognitive decline (ARCD), stroke, traumatic brain injury, AIDS associated dementia, and dementia associated with depression, anxiety and psychosis (including schizophrenia and hallucinatory disorders).

20 Attention Deficit Disorders, e.g., attention deficit disorder (ADD) and attention deficit and hyperactivity disorder (ADHD).

Speech disorders, e.g., motor tic, clonic stuttering, dysfluency, speech blockage, dysarthria, Tourette's Syndrome and logospasm.

Compounds and compositions provided herein can also be used to improve short-term memory 25 (working memory) in a patient. A preferred therapeutically effective amount of a compound for improving short-term memory loss is an amount sufficient to result in a statistically significant improvement in any standard test of short-term memory function, including forward digit span and serial rote learning. For example, such a test may be designed to evaluate the ability of a patient to recall words or letters. Alternatively, a more complete neurophysical evaluation may be used to assess 30 short-term memory function. Patients treated in order to improve short-term memory may, but need not, have been diagnosed with memory impairment or be considered predisposed to development of such impairment.

In a separate aspect, the present invention provides methods for potentiating the action (or therapeutic effect) of other CNS agent(s). Such methods comprise administering a therapeutically 35 effective amount of a compound provided herein in combination with a therapeutically effective amount of another CNS agent. Such other CNS agents include, but are not limited to the following: for anxiety, serotonin receptor (e.g., 5-HT_{1A}) agonists and antagonists; for anxiety and depression,

neurokinin receptor antagonists or corticotropin releasing factor receptor (CRF₁) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as Alzheimer's dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. Within certain embodiments, the present invention provides a method of potentiating the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) by co-administering a therapeutically effective amount of a GABA_A agonist compound provided herein in combination with an SSRI. A therapeutically effective amount of compound, when co-administered with another CNS agent, is an amount sufficient to result in a detectable change in patient symptoms, when compared to a patient treated with the other CNS agent alone.

The present invention also pertains to methods of inhibiting the binding of benzodiazepine compounds (*i.e.*, compounds that comprise the benzodiazepine ring structure), such as RO15-1788 or GABA, to GABA_A receptor. Such methods involve contacting cells expressing GABA_A receptor with a concentration of compound provided herein that is sufficient to inhibit the binding of GABA_A receptor ligand to GABA_A receptor *in vitro*, as determined using the assay described in Example 4. This method includes, but is not limited to, inhibiting the binding of benzodiazepine compounds to GABA_A receptors *in vivo* (*e.g.*, in a patient given an amount of a GABA_A receptor modulator provided herein that results in a concentration of compound in cerebrospinal fluid that is sufficient to inhibit the binding of benzodiazepine compounds or GABA to GABA_A receptor *in vitro*). In one embodiment, such methods are useful in treating benzodiazepine drug overdose. The amount of GABA_A receptor modulator that is sufficient to inhibit the binding of a benzodiazepine compound to GABA_A receptor may be readily determined via a GABA_A receptor binding assay as described in Example 4.

Within separate aspects, the present invention provides a variety of *in vitro* uses for the GABA_A receptor modulators provided herein. For example, such compounds may be used as probes for the detection and localization of GABA_A receptors, in samples such as tissue sections, as positive controls in assays for receptor activity, as standards and reagents for determining the ability of a candidate agent to bind to GABA_A receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such assays can be used to characterize GABA_A receptors in living subjects. Such compounds are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to GABA_A receptor.

Within methods for determining the presence or absence of GABA_A receptor in a sample, a sample may be incubated with a compound as provided herein under conditions that permit binding of the compound to GABA_A receptor. The amount of compound bound to GABA_A receptor in the sample is then detected. For example, the compound may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with the sample (which may be, for example, a preparation of cultured cells, a tissue preparation or a fraction thereof). A suitable incubation time may generally be determined by assaying the level of binding that occurs over a period of time. Following incubation, unbound compound is removed, and

bound compound detected using any method suitable for the label employed (e.g., autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample may be simultaneously contacted with radiolabeled compound and a greater amount of unlabeled compound. Unbound labeled and unlabeled compound is then removed in the same fashion, and bound label is detected. A greater amount of detectable label in the test sample than in the control indicates the presence of GABA_A receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of GABA_A receptors in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

For example, compounds provided herein may be used for detecting GABA_A receptors in cell or tissue samples. This may be done using matched cell or tissue samples that have not previously been contacted with a GABA_A receptor modulator, at least one of which is prepared as an experimental sample and at least one of which is prepared as a control sample. An experimental sample is prepared by contacting (under conditions that permit binding of RO15-1788 to GABA_A receptors within cell and tissue samples) a sample with a detectably-labeled compound of Formula I. A control sample is prepared in the same manner as the experimental sample, except that it is also contacted with unlabelled compound at a molar concentration that is greater than the concentration of labeled modulator.

The experimental and control samples are then washed to remove unbound detectably-labeled compound. The amount of remaining bound detectably-labeled compound is then measured and the amount of detectably-labeled compound in the experimental and control samples is compared. The detection of a greater amount of detectable label in the washed experimental sample(s) than in the washed control sample(s) demonstrates the presence of GABA_A receptor in the experimental sample.

The detectably-labeled GABA_A receptor modulator used in this procedure may be labeled with a radioactive label or a directly or indirectly luminescent label. When tissue sections are used in this procedure and the label is a radiolabel, the bound, labeled compound may be detected autoradiographically.

Compounds provided herein may also be used within a variety of well known cell culture and cell separation methods. For example, compounds may be linked to the interior surface of a tissue culture plate or other cell culture support, for use in immobilizing GABA_A receptor-expressing cells for screens, assays and growth in culture. Such linkage may be performed by any suitable technique, such as the methods described above, as well as other standard techniques. Compounds may also be used to facilitate cell identification and sorting *in vitro*, permitting the selection of cells expressing a GABA_A receptor. Preferably, the compound(s) for use in such methods are labeled as described herein. Within one preferred embodiment, a compound linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed by fluorescence activated cell sorting (FACS).

Within other aspects, methods are provided for modulating binding of ligand to a GABA_A receptor *in vitro* or *in vivo*, comprising contacting a GABA_A receptor with a sufficient amount of a GABA_A receptor modulator provided herein, under conditions suitable for binding of ligand to the receptor. The GABA_A receptor may be present in solution, in a cultured or isolated cell preparation or within a patient. Preferably, the GABA_A receptor is present in the brain of a mammal. In general, the amount of compound contacted with the receptor should be sufficient to modulate ligand binding to GABA_A receptor *in vitro* within, for example, a binding assay as described in Example 4.

Also provided herein are methods for altering the signal-transducing activity of cellular GABA_A receptor (particularly the chloride ion conductance), by contacting GABA_A receptor, either *in vitro* or *in vivo*, with a sufficient amount of a compound as described above, under conditions suitable for binding of Flumazenil to the receptor. The GABA_A receptor may be present in solution, in a cultured or isolated cell or cell membrane preparation or within a patient, and the amount of compound may be an amount that would be sufficient to alter the signal-transducing activity of GABA_A receptor *in vitro*. In certain embodiments, the amount or concentration of compound contacted with the receptor should be sufficient to modulate Flumazenil binding to GABA_A receptor *in vitro* within, for example, a binding assay as described in Example 4. An effect on signal-transducing activity may be detected as an alteration in the electrophysiology of the cells, using standard techniques. The amount or concentration of a compound that is sufficient to alter the signal-transducing activity of GABA_A receptors may be determined via a GABA_A receptor signal transduction assay, such as the assay described in Example 5. The cells expressing the GABA receptors *in vivo* may be, but are not limited to, neuronal cells or brain cells. Such cells may be contacted with one or more compounds provided herein through contact with a body fluid containing the compound, for example through contact with cerebrospinal fluid. Alteration of the signal-transducing activity of GABA_A receptors in cells *in vitro* may be determined from a detectable change in the electrophysiology of cells expressing GABA_A receptors, when such cells are contacted with a compound of the invention in the presence of GABA.

Intracellular recording or patch-clamp recording may be used to quantitate changes in electrophysiology of cells. A reproducible change in behavior of an animal given a compound of the invention may also be taken to indicate that a change in the electrophysiology of the animal's cells expressing GABA_A receptors has occurred.

PREPARATION OF COMPOUNDS

Compounds provided herein may generally be prepared using standard synthetic methods. Starting materials are generally readily available from commercial sources, such as Sigma-Aldrich Corp. (St. Louis, MO), or may be prepared as described herein. Representative procedures suitable for the preparation of compounds of Formula I are outlined in the following Schemes, which are not to be construed as limiting the invention in scope or spirit to the specific reagents and conditions shown in them. Those having skill in the art will recognize that the reagents and conditions may be varied and

additional steps employed to produce compounds encompassed by the present invention. In some cases, protection of reactive functionalities may be necessary to achieve the desired transformations. In general, such need for protecting groups, as well as the conditions necessary to attach and remove such groups, will be apparent to those skilled in the art of organic synthesis. Unless otherwise stated in the schemes below, the variables are as defined in Formula I.

Abbreviations used the following Schemes and the accompanying Examples are as follows:

BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Bu butyl

CDCl₃ deuterated chloroform

δ chemical shift

DCM dichloromethane

DME ethylene glycol dimethyl ether

DMF N,N-dimethylformamide

DMSO dimethylsulfoxide

EtOAc ethyl acetate

EtOH ethanol

HOAc acetic acid

HPLC high pressure liquid chromatography

¹H NMR proton nuclear magnetic resonance

Hz hertz

LC/MS liquid chromatography/mass spectrometry

MeOH methanol

MS mass spectrometry

M+1 mass + 1

mCPBA m-chloroperoxybenzoic acid

OAc acetate

Pd(Ph₃P)₂Cl₂ dichlorobis(triphenylphosphine) palladium (II)

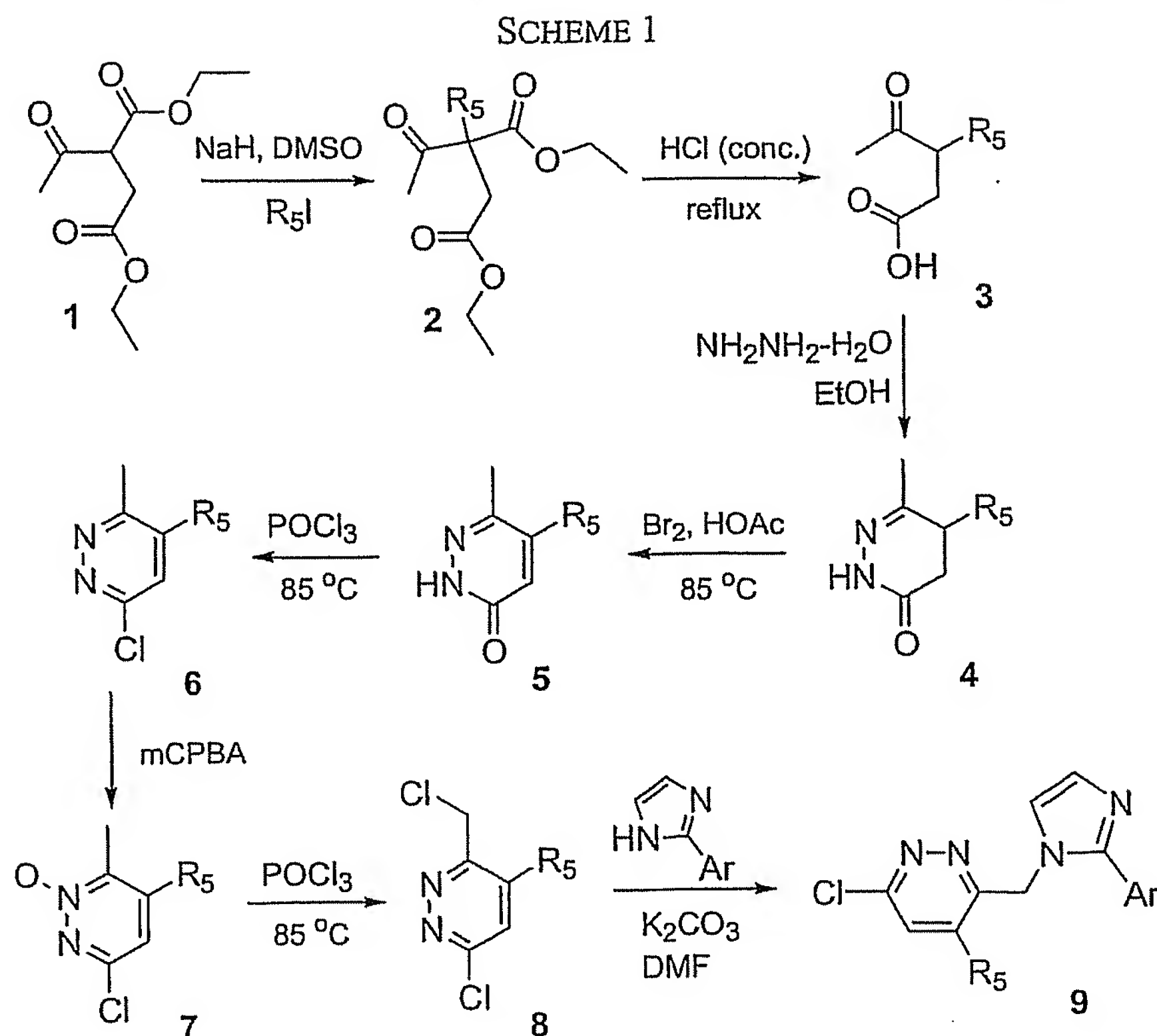
Pr propyl

PTLC preparative thin layer chromatography

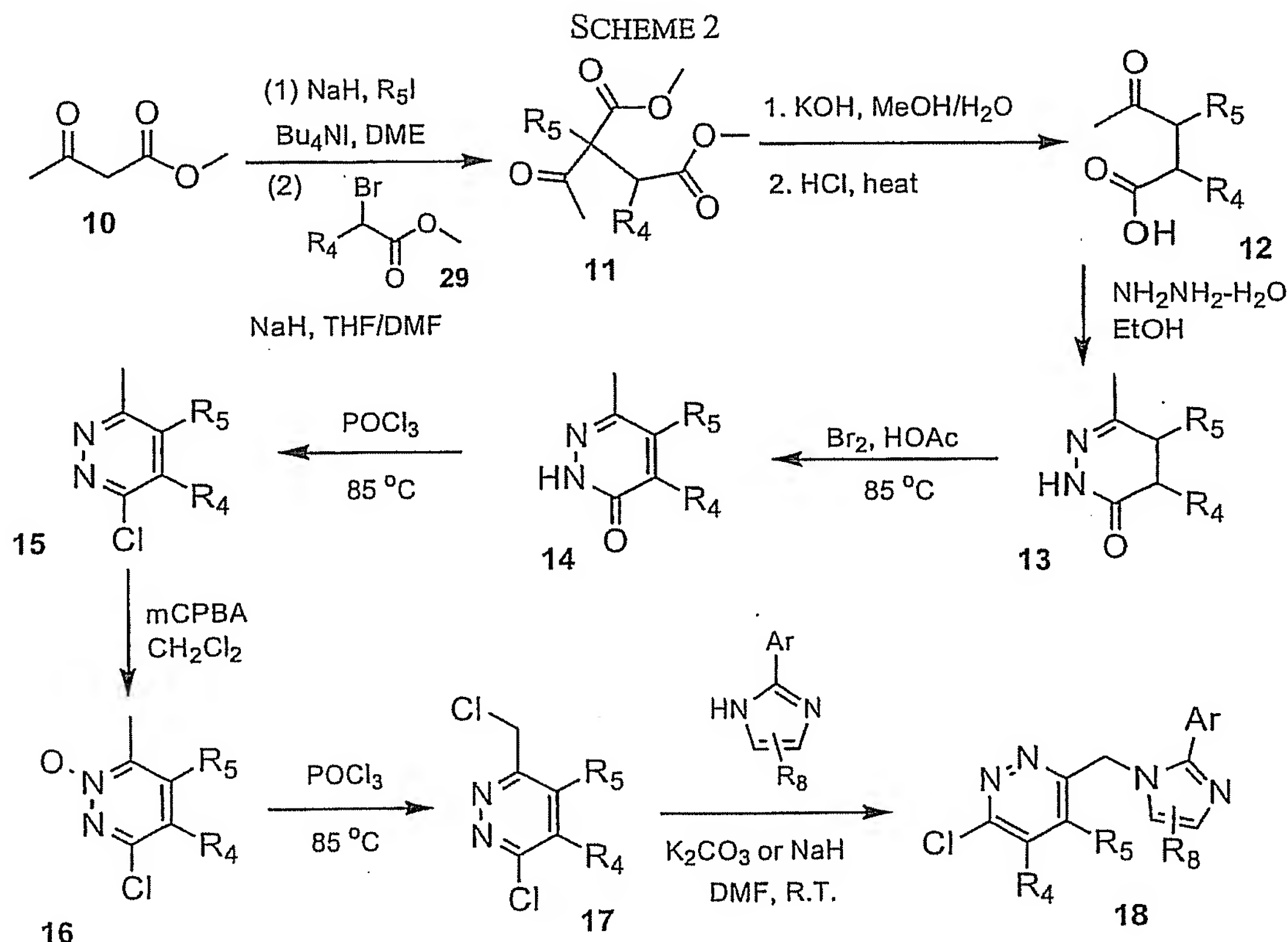
R.T. room temperature

THF tetrahydrofuran

TLC thin layer chromatography

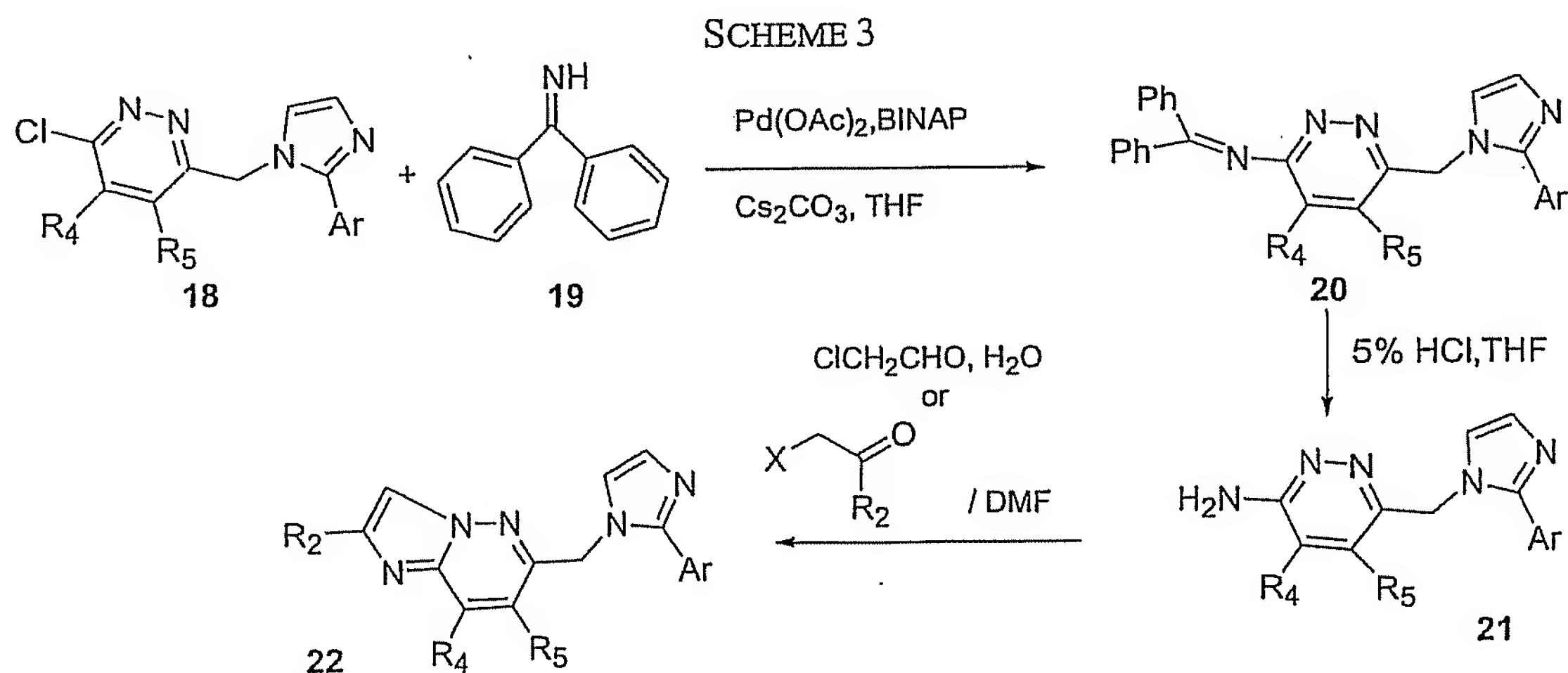


Scheme 1 illustrates a synthetic route to compounds of formula 9. Alkylation of 2-acetyl-succinic acid diethyl ester gives 2, which upon hydrolysis and decarboxylation affords acid 3. Treatment of 3 with hydrazine gives 4, which aromatizes on treatment with bromine in acetic acid to pyridazinone 5. 5 is converted to chloropyridazine 6 upon treatment with POCl_3 . N-oxidation of 6 with mCPBA affords N-oxide 7, which is reacted with POCl_3 to give chloromethylpyridazine 8. 8 is coupled with an arylimidazole under basic conditions in DMF to give 9. The choice of base used in this step depends on the acidic nature of the arylimidazole.



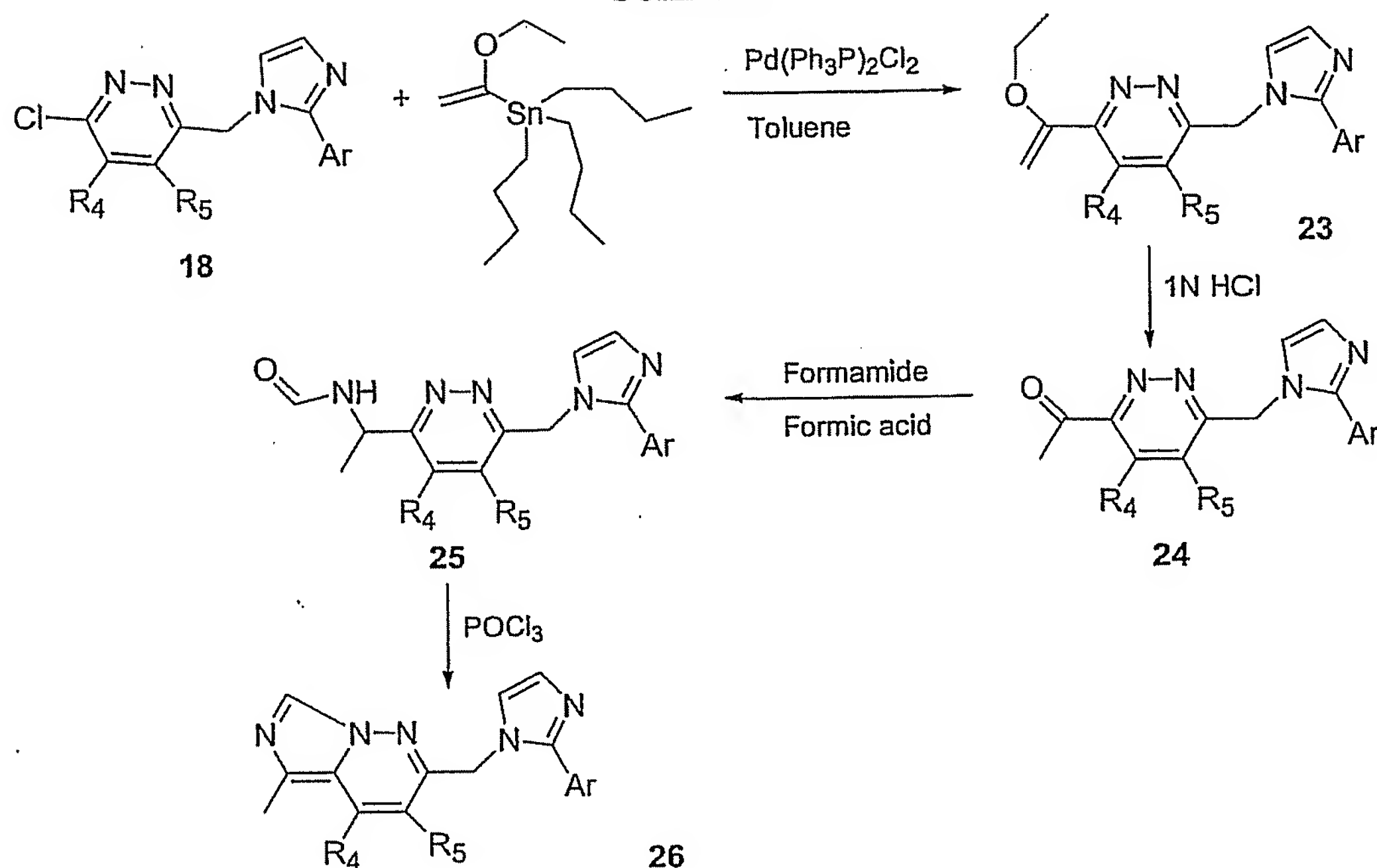
Scheme 2 illustrates the synthesis of compounds of formula 18 (R_4 = alkyl). Double alkylation of acetoacetate 10 gives 11, which upon hydrolysis and decarboxylation affords R_4 substituted acid 12.

5 Similar to the synthesis of 9, 18 is prepared from 12.



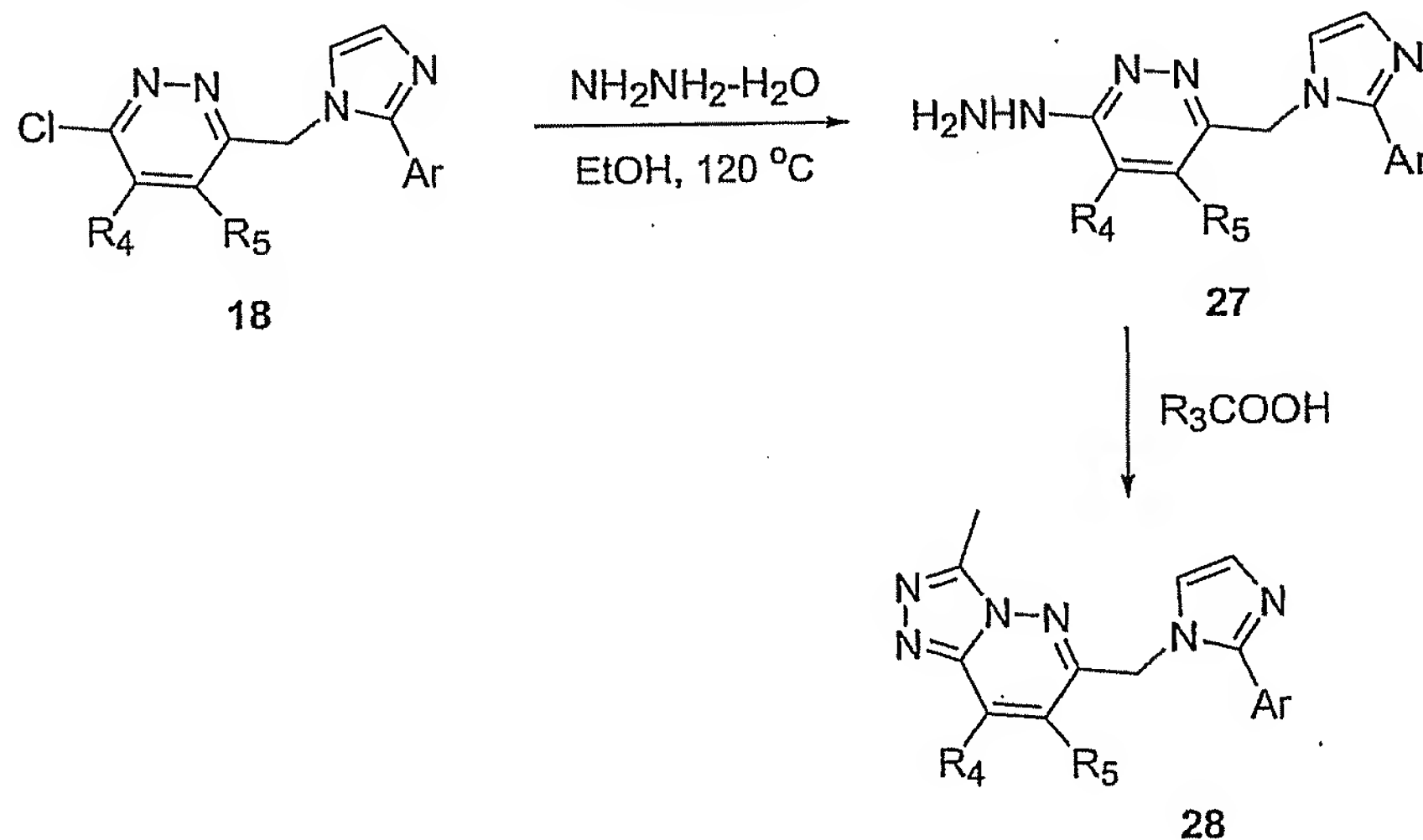
Scheme 3 illustrates the synthesis of imidazolopyridazines 22. Reaction of chloropyridazine 18 with benzophenone imine 19 in the presence of Pd(OAc)_2 and BINAP provides 20. Aminopyridazine 21 is obtained from the hydrolysis of 20. Reaction of aminopyridazine 21 with an appropriate α -halo aldehyde or ketone gives imidazo[1,2-b]pyridazine 22.

SCHEME 4



Scheme 4 illustrates the synthesis of compounds of formula 26. Chloropyridazine 18 reacts with tributyltinvinylether in the presence of $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ to provide vinyl ether 23, which is hydrolyzed to ketone 24. Reaction of acetylpyridazines 24 with formic acid in formamide followed by treatment with POCl_3 provides imidazolopyridazine 26.

SCHEME 5



Scheme 5 illustrates the synthesis of triazolopyridazines for formula 28. Treatment of chloropyridazine 18 with hydrazine affords hydrazide 27, which upon treatment with a carboxylic acid gives 28.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (e.g., ^{14}C), hydrogen (e.g., ^3H), sulfur (e.g., ^{35}S) or iodine (e.g., ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in

tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. Starting materials and intermediates described herein may generally be obtained from commercial sources, prepared from commercially available organic compounds using well known synthetic methods.

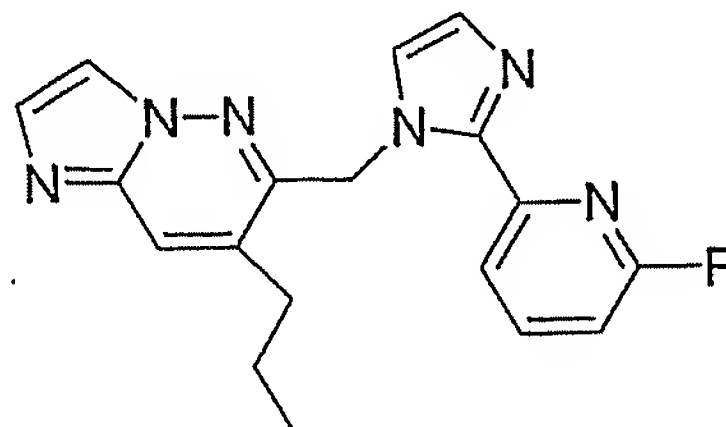
EXAMPLES

Starting materials and various intermediates described in the following Examples may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using known synthetic methods. Representative examples of methods suitable for preparing certain intermediates are also set forth below.

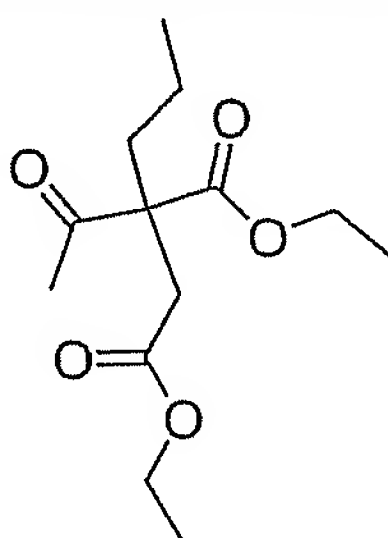
In the following Examples, LC/MS conditions for the characterization of the compounds herein are:

1. Analytical HPLC/MS instrumentation: Analyses are performed using a Waters 600 series pump (Waters Corp., Milford, MA), a Waters 996 Diode Array Detector and a Gilson 215 auto-sampler (Gilson Inc, Middleton, WI), Micromass® LCT time-of-flight electrospray ionization mass analyzer. Data are acquired using MassLynx™ 4.0 software, with OpenLynx Global Server™, OpenLynx™ and AutoLynx™ processing.
2. Analytical HPLC conditions: 4.6x50mm, Chromolith™ SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany); UV 10 spectra/sec, 220-340nm summed; flow rate 6.0 mL/min; injection volume 1 µl;
Gradient conditions - mobile phase A is 95% water, 5% MeOH with 0.05% TFA; mobile phase B is 95% MeOH, 5% water with 0.025% TFA, and the gradient is 0-0.5 minutes 10-100% B, hold at 100%B to 1.2 minutes, return to 10%B at 1.21 minutes inject-to-inject cycle time is 2.15 minutes.
3. Analytical MS conditions: capillary voltage 3.5kV; cone voltage 30V; desolvation and source temperature are 350°C and 120°C, respectively; mass range 181-750 with a scan time of 0.22 seconds and an inter scan delay of 0.05 minutes.

EXAMPLE 1. SYNTHESIS OF IMIDAZO[1,2-B]PYRIDAZINES

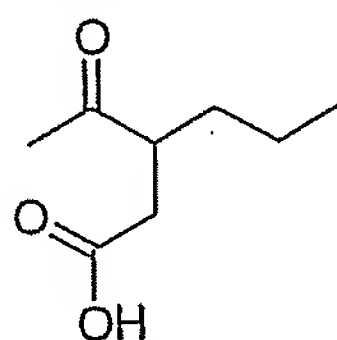
A. 6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE
(111)

5 Step 1. Preparation of 2-Acetyl-2-propyl-succinic acid diethyl ester (100)



To a solution of 2-acetyl-succinic acid diethyl ester (30 g, 139 mmol) in DMSO (250 ml) is added NaH (5.8 g, 60% in mineral oil, 145 mmol) in 10 portions over a period of 1 hour. The resulting solution is stirred at room temperature for another 1.5 hours. PrI (17.1 ml, 174 mmol) is added slowly over the period of 45 minutes and the resulting solution is stirred at room temperature overnight. Water (500 ml) is added, the solution is saturated with NaCl and extracted with EtOAc (3 x 250 ml). The combined extracts are washed with brine (400 ml), dried over Na₂SO₄ and evaporated *in vacuo*. The resulting yellow oil is used in the next step without further purification.

Step 2. Preparation of 3-Acetyl-hexanoic acid (101)

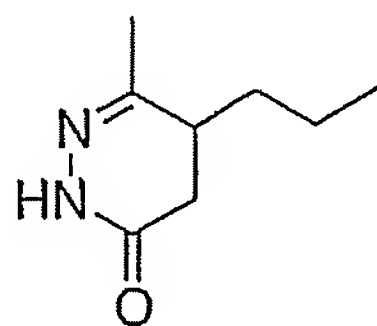


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To 35g of the oil, 2-acetyl-2-propyl-succinic acid diethyl ester, is added concentrated HCl (200 ml). The mixture is refluxed (oil bath 105°C) overnight and to it is added brine (100 ml). The mixture is extracted with EtOAc (4 x 150 ml) and the combined extracts are extracted with 2N aqueous NaOH solution (4 x 100 ml). The NaOH solution is then cooled to 0°C and acidified with concentrated HCl. The mixture is extracted with EtOAc (4 x 200 ml) and the combined extracts are washed with brine (200 ml), dried (Na₂SO₄) and evaporated *in vacuo*, which provides a yellow oil.

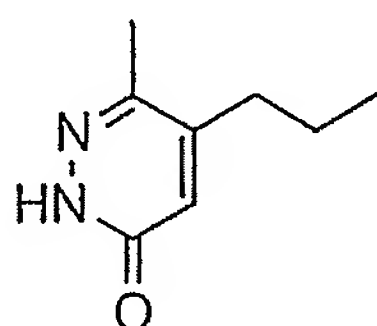
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Step 3. Preparation of 6-Methyl-5-propyl-4,5-dihydro-2H-pyridazin-3-one (102)



5 To a solution of 3-acetyl-hexanoic acid (18.8 g, 119 mmol) in EtOH (150 ml) is added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (6.94 ml, 143 mmol) and the mixture is refluxed (oil bath 85°C) for 4 hours. The solvent is removed *in vacuo* and to the residue is added water (100 ml) and EtOAc (100 ml). The layers are separated and the aqueous layer is extracted with EtOAc (3 x 100ml). The combined extracts are washed with brine (150 ml), dried (Na_2SO_4) and evaporated. The resulting light yellow oil is used in the next step without further purification.

Step 4. Preparation of 6-Methyl-5-propyl-pyridazin-3-one (103)

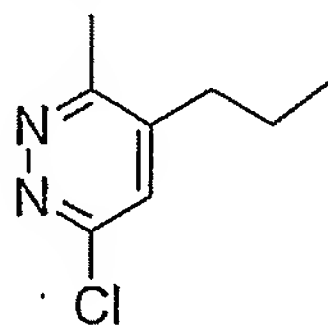


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To a solution of 6-methyl-5-propyl-4,5-dihydropyridazin-3-one (16.7 g, 108 mmol) in HOAc (200 ml) heated to 85°C is added Br_2 (5.5 ml, 108 mmol) dropwise. After the addition, the mixture is stirred at 85°C for 1 hour. The solvent is removed *in vacuo* and the residue is dissolved in EtOAc (250 ml) and washed with NaHCO_3 (200 ml) followed by $\text{Na}_2\text{S}_2\text{O}_3$ saturated solution (50 ml) and brine (200 ml). The organic phase is dried (Na_2SO_4) and evaporated. The resulting yellow solid is used in the next step without further purification.

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Step 5. Preparation of 6-Chloro-3-methyl-4-propyl-pyridazine (104)

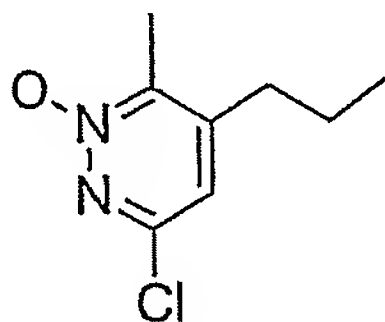


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The mixture of 6-methyl-5-propyl-4,5-dipyridazin-3-one (15.3 g, 100 mmol) and POCl_3 (125 ml) is heated at 85°C for 4 hours. The solvent is removed and the residue is dissolved in EtOAc (200 ml). The solution is cooled by ice bath and a saturated aqueous solution of NaHCO_3 is added carefully until the aqueous layer became basic. The layers are separated and the aqueous layer is extracted with EtOAc (150 ml). The combined organic extracts are washed with brine (150 ml), dried (Na_2SO_4) and evaporated. Flash column separation of the residue with 4:1 hexane:EtOAc provides the product as a light yellow oil.

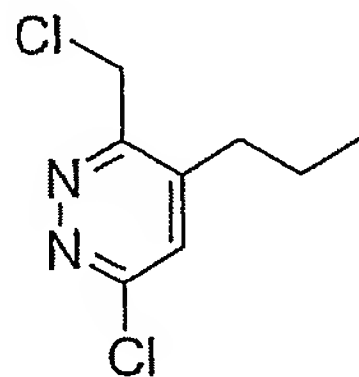
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Step 6. Preparation of 6-Chloro-3-methyl-4-propyl-pyridazine 2-oxide (105)



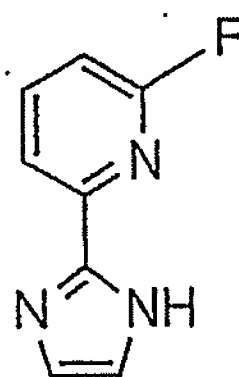
To a solution of 6-chloro-3-methyl-4-propyl-pyridazine (8.03 g, 47.06 mmol) in CH_2Cl_2 (200 ml) is added mCPBA (11.6 g, 77%, 51.77 mmol). The mixture is stirred at room temperature overnight. Saturated K_2CO_3 aqueous solution (50 ml) is added and the layers are separated. The organic layer is then washed with brine (100 ml) and dried (Na_2SO_4) and evaporated, which provides the product as a light yellow oil.

Step 7. Preparation of 6-Chloro-3-chloroethyl-4-propyl-pyridazine (106)



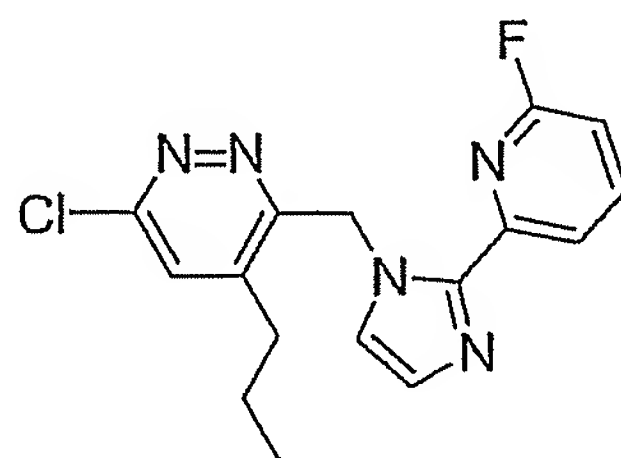
A mixture of 6-chloro-3-methyl-4-propyl-pyridazine 2-oxide (9.3 g, 50 mmol) and POCl_3 (80 ml) is heated at 85°C for 4 hours. The solvent is removed and the residue is dissolved in EtOAc (200 ml). The solution is cooled by ice bath and to it is carefully added saturated aqueous solution of NaHCO_3 until the aqueous layer is basic. The layers are separated and the aqueous layer is extracted with EtOAc (150 ml). The combined organic extracts are washed with brine (200 ml), dried (Na_2SO_4) and evaporated. Flash column separation of the residue with 5:1 Hexanes:EtOAc provides the title compound as a light yellow oil.

Step 8. Preparation of 6-Fluoro-2-(1H-imidazol-2-yl)-pyridine (107)



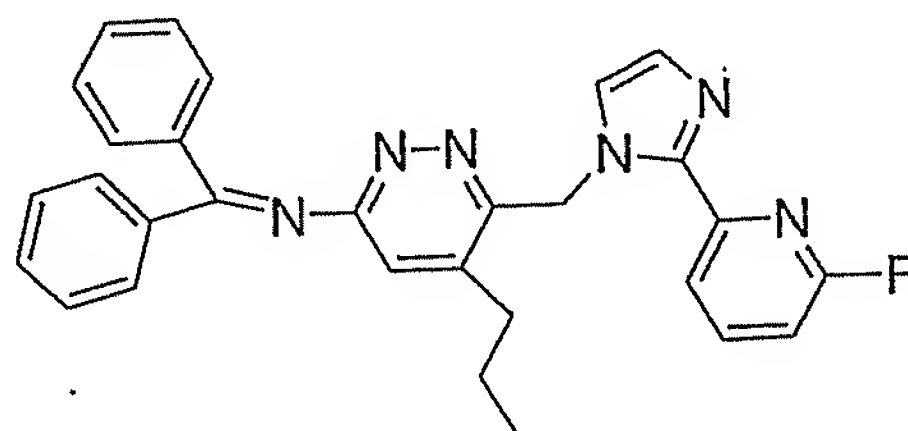
Glyoxal (40% w/w H_2O , 16.0 g, 0.110 mol) and ammonium hydroxide (con. 29 mL) are added to a solution of 6-fluoro-pyridine-2-carbaldehyde (11.5 g, 0.092 mol) in MeOH (450 mL) at 0°C . The mixture is allowed to warm gradually to room temperature over an 18 hour period. The solvent is removed. Water (100 mL) is added to the residue and the mixture is extracted with methylene chloride (5 x 150 mL). The combined organic layers are washed with brine (2 x 100 mL), dried, and solvent removed. The crude is triturated with ethyl ether (200 mL) to give the title compound as a solid.

Step 9. Preparation of 6-Chloro-3-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-propyl-pyridazine (108)



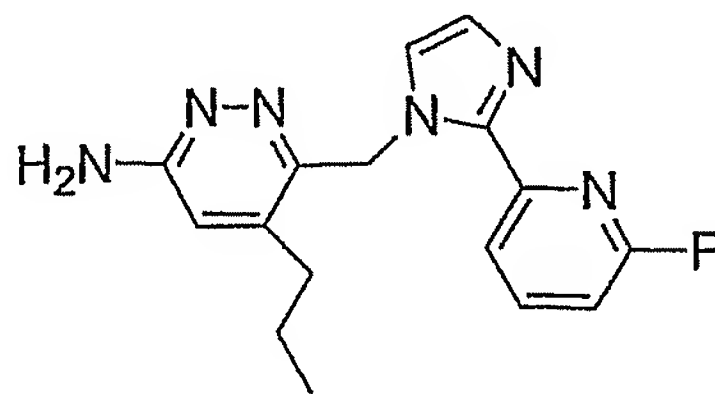
To a mixture of 6-chloro-3-chloroethyl-4-propyl-pyridazine (5.01 g, 24.43 mmol), 2-fluoro-6-(imidazol-2-yl)-pyridine (3.99 g, 24.43 mmol) and anhydrous K_2CO_3 (10.2 g, 73.3 mmol) is added DMF (30 ml) and the mixture is stirred at room temperature overnight. The solvent is removed *in vacuo* and to the residue is added water (30 ml) and EtOAc (30 ml) and the layers are separated. The aqueous layer is extracted with EtOAc (3 x 30 ml) and the combined extracts are washed with brine (30 ml), dried (Na_2SO_4) and evaporated, which provides a light brown solid. The solid is washed twice with 1:1 hexane, ether (25 ml), which provides the title compound as a light yellow solid.

Step 10. Preparation of Benzhydrylidene-{6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridin-3-yl}-amine (109)



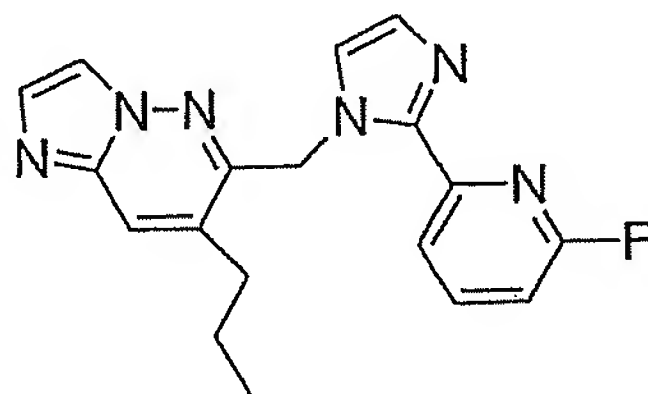
A round-bottom sealed tube is purged with nitrogen and charged with $Pd(OAc)_2$ (31mg, 5%), BINAP (94mg, 5%), and dry THF. The mixture is flushed with N_2 for approximately 5 minutes, while stirring, 6-chloro-3-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-propyl-pyridazine (0.92g, 2.78mmol), benzophenone imine (0.5g, 3.0mmol) and Cs_2CO_3 (1.82g, 3.0 mmol, 2eq.) are added, and the mixture is heated at $90^\circ C$ until the starting material has been consumed. The mixture is cooled to room temperature. THF is removed and EtOAc (40 ml) is added, the mixture is washed with water (10ml), brine (10 ml) and dried. The evaporation of solvent gives the crude product, which is purified by column with 2:1 EtOAc: hexane to give the title compound. 1H NMR δ ($CDCl_3$) 8.16 (d, 1H, $J = 6Hz$), 7.83 (m, 2H,), 7.04-7.60 (m, 10H), 6.80-6.92 (m, 2H), 6.60 (s, 1H), 6.18 (s, 2H), 2.43 (t, 2H, $J = 5.4 Hz$), 1.27 (m, 2H), 0.66 (t, 3H, $J = 5.4 Hz$). LC/MS ($M+1$) 477.2.

Step 11. Preparation of 6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-ylamine (110)



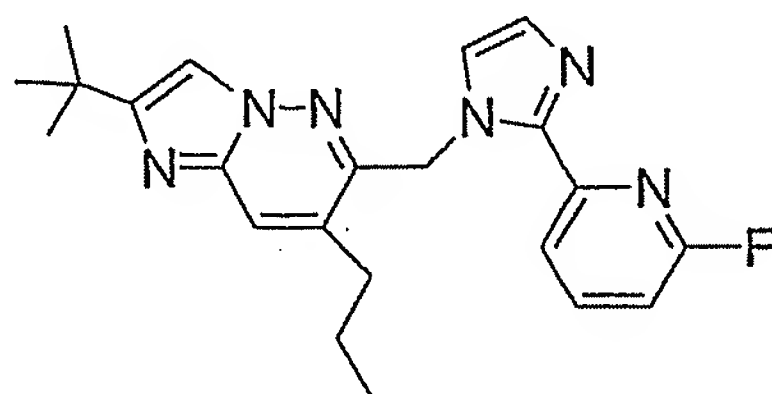
Benzhydrylidene-{6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridin-3-yl}-amine (0.4g) is dissolved in THF (20 mL) at room temperature. 5% of HCl solution (10 mL) is added, and the mixture is stirred at room temperature for 30 minutes. TLC indicates the completion of the reaction. THF is removed and the mixture is neutralized with sat. NaHCO₃. The solution is extracted with chloroform (30 mL x 3). The organic phase is dried over MgSO₄. The solvent is removed, leaving a white solid that is washed with ether to yield the title compound. ¹H NMR δ (CDCl₃) 8.16 (d, 1H, J = 6Hz), 7.83 (q, 1H, J = 6 Hz), 7.11 (s, 1H), 7.06 (s, 1H), 6.85 (dd, 1H, J = 6, 1.8Hz), 6.54 (s, 1H), 6.16 (s, 2H), 2.47 (t, 2H, J = 5.4 Hz), 1.43 (hex, 2H, J = 5.4 Hz), 0.81 (t, 3H, J = 5.4 Hz). LC/MS (M+1) 313.1.

Step 12. Preparation of 6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine (111)



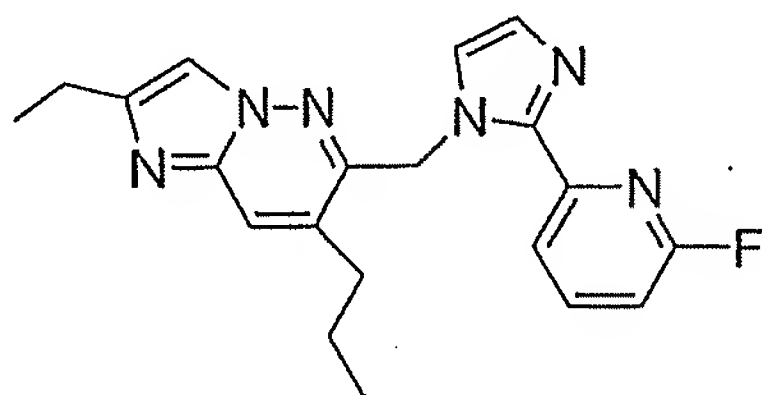
6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-ylamine (40 mg) and 50% of chloroacetaldehyde in water (0.5 ml) and DMF (5 mL) is heated at 70°C overnight. EtOAc (20 mL) is added, and the mixture is washed with sat. NaHCO₃ and dried. The solvent is removed *in vacuo* and the crude is purified by PTLC with 5% MeOH in DCM to give the title compound. ¹H NMR δ (CDCl₃) 8.16 (d, 1H, J = 6Hz), 7.83 (q, 1H, J = 6 Hz), 7.73 (s, 1H), 7.71 (s, 1H), 7.64 (s, 1H), 7.21 (s, 1H), 7.07 (s, 1H), 6.78 (dd, 1H, J = 6, 1.8Hz), 6.09 (s, 2H), 2.68 (t, 2H, J = 5.4 Hz), 1.69 (hex, 2H, J = 5.4 Hz), 0.95 (t, 3H, J = 5.4 Hz). LC/MS (M+1) 337.1.

B. 2-TERT-BUTYL-6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE (112)



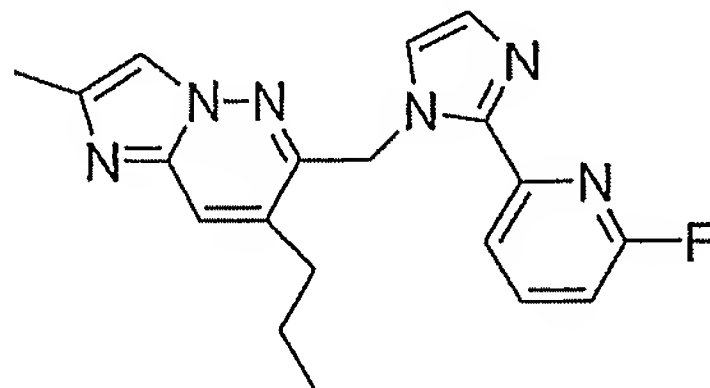
A mixture of 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-ylamine (20 mg) and 1-bromopinacolone (13.8 mg) in DMF (5 mL) is heated at 70°C overnight. The remainder of the synthesis is essentially as described in Example 1A, resulting in the title compound. ^1H NMR δ (CDCl_3) 8.16 (dd, 1H, $J = 7.8, 2.1$ Hz), 7.83 (q, 1H, $J = 7.8$ Hz), 7.67 (s, 1H), 7.54 (s, 1H), 7.21 (d, 1H, $J = 0.9$ Hz), 7.05 (d, 1H, $J = 0.9$ Hz), 6.81 (dd, 1H, $J = 7.8, 2.1$ Hz), 6.09 (s, 2H), 2.66 (t, 2H, $J = 5.4$ Hz), 1.66 (hex, 2H, $J = 5.4$ Hz), 1.37 (s, 9H), 0.95 (t, 3H, $J = 5.4$ Hz). LC/MS ($M+1$) 393.26.

C. 2-ETHYL-6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE (113)



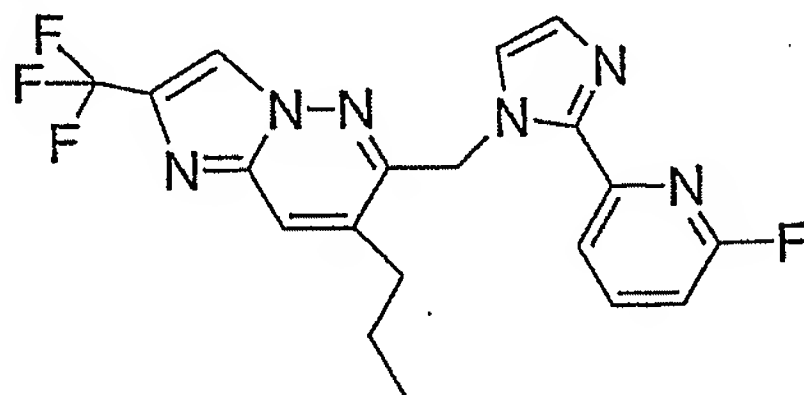
A mixture of 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-ylamine (48mg) and 1-bromo-2-butanone (50 mg) in DMF (5 mL) is heated at 70°C overnight. The remainder of the synthesis is essentially as described in Example 1A, resulting in the title compound. ^1H NMR δ (CDCl_3) 8.16 (dd, 1H, $J = 7.8, 2.1$ Hz), 7.83 (q, 1H, $J = 7.8$ Hz), 7.60 (s, 1H), 7.53 (s, 1H), 7.19 (s, 1H), 7.05 (s, 1H), 6.81 (dd, 1H, $J = 7.8, 2.1$ Hz), 6.07 (s, 2H), 2.79 (q, 2H, $J = 7.8$ Hz), 2.65 (t, 2H, $J = 5.4$ Hz), 2.45 (s, 3H), 1.63 (hex, 2H, $J = 5.4$ Hz), 1.32 (t, 2H, $J = 7.8$ Hz), 0.95 (t, 3H, $J = 5.4$ Hz). LC/MS ($M+1$) 365.18.

D. 2-METHYL-6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE (114)



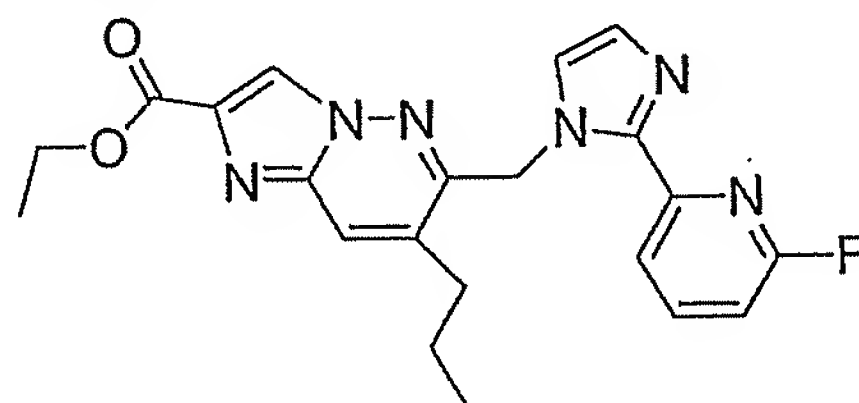
A mixture of 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-ylamine (20 mg) and chloroacetone (7.7 mg) in DMF (5 mL) is heated at 100°C for 5 hours. The remainder of the synthesis is essentially as described in Example 1A, resulting in the title compound. ^1H NMR δ (CDCl_3) 8.16 (dd, 1H, $J = 7.8, 2.1$ Hz), 7.83 (q, 1H, $J = 7.8$ Hz), 7.64 (s, 1H), 7.51 (s, 1H), 7.20 (s, 1H), 7.05 (s, 1H), 6.81 (dd, 1H, $J = 7.8, 2.1$ Hz), 6.08 (s, 2H), 2.66 (t, 2H, $J = 5.4$ Hz), 2.45 (s, 3H), 1.63 (hex, 2H, $J = 5.4$ Hz), 0.95 (t, 3H, $J = 5.4$ Hz). LC/MS ($M+1$) 351.20.

E. 6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-2-TRIFLUOROMETHYL-IMIDAZO[1,2-B]PYRIDAZINE (115)



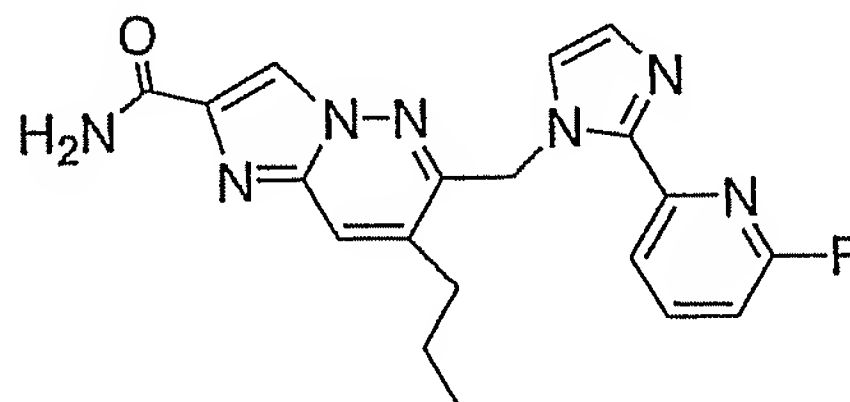
A mixture of 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-ylamine (32 mg) and bromotrifluoroacetone (23 mg) in DMF (5mL) is heated at 70°C overnight. The remainder of the synthesis is essentially as described in Example 1A, resulting in the title compound. ^1H NMR δ (CDCl₃) 8.16 (dd, 1H, J = 7.8, 2.1 Hz), 7.97 (s, 1H), 7.82 (q, 1H, J = 7.8 Hz), 7.75 (s, 1H), 7.20 (s, 1H), 7.08 (s, 1H), 6.81 (dd, 1H, J = 7.8, 2.1 Hz), 6.07 (s, 2H), 2.76 (t, 2H, J = 5.4 Hz), 1.74 (hex, 2H, J = 5.4 Hz), 1.04 (t, 3H, J = 5.4 Hz). LC/MS (M+1) 405.18.

F. 6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE-2-CARBOXYLIC ACID ETHYL ESTER (116)



A mixture of 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-ylamine (20 mg) and ethyl bromopyruvate (15 mg) in DMF (5mL) is heated at 90°C for 7 hours. The remainder of the synthesis is essentially as described in Example 1A, resulting in the title compound. ^1H NMR δ (CDCl₃) 8.25 (s, 1H), 8.16 (dd, 1H, J = 7.8, 2.1 Hz), 7.80 (q, 1H, J = 7.8 Hz), 7.75 (s, 1H), 7.23 (d, 1H, J = 0.9 Hz), 7.09 (d, 1H, J = 0.9 Hz), 6.78 (dd, 1H, J = 7.8, 2.1 Hz), 6.08 (s, 2H), 4.42 (q, 2H, J = 6.9 Hz), 2.74 (t, 2H, J = 5.4 Hz), 1.71 (hex, 2H, J = 5.4 Hz), 1.40 (t, 3H, J = 6.9 Hz), 0.99 (t, 3H, J = 5.4 Hz). LC/MS (M+1) 409.22.

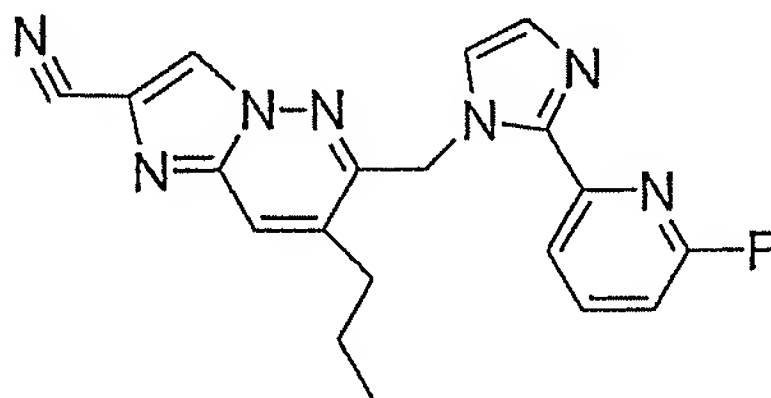
G. 6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE-2-CARBOXYLIC ACID AMIDE (117)



6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine-2-carboxylic acid ethyl ester (50 mg) is dissolved in EtOH (10 mL). Ammonium hydroxide (2 mL) is added. The mixture is heated in a sealed tube at 60°C for 10 hours. The solvent is removed to give the

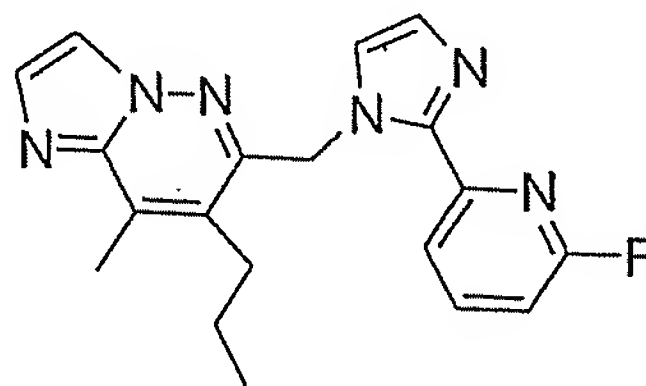
title compound. ^1H NMR δ (CDCl_3) 8.25 (s, 1H), 8.16 (dd, 1H, $J = 7.8, 2.1$ Hz), 7.83 (q, 1H, $J = 7.8$ Hz), 7.66 (s, 1H), 7.23 (d, 1H, $J = 0.9$ Hz), 7.14 (br, 1H), 7.09 (d, 1H, $J = 0.9$ Hz), 6.78 (dd, 1H, $J = 7.8, 2.1$ Hz), 6.09 (s, 2H), 5.51 (br, 1H), 2.73 (t, 2H, $J = 5.4$ Hz), 1.71 (hex, 2H, $J = 5.4$ Hz), 0.99 (t, 3H, $J = 5.4$ Hz). LC/MS ($M+1$) 380.14.

- 5 H. 6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE-2-CARBONITRILE (118)

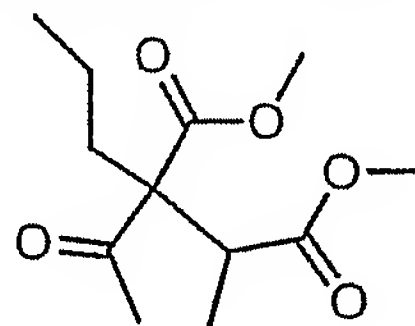


- 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine-2-carboxylic acid amide (20 mg) is dissolved in pyridine (1 mL). The mixture is cooled to 0°C , and POCl_3 (0.2 mL) is added dropwise. The mixture is stirred for two hours, quenched with ice and extracted with DCM. The organic phase is dried over MgSO_4 , and the solvent is removed to give the crude product. After purification with PTLC (5% MeOH in DCM), the title compound is obtained. ^1H NMR δ (CDCl_3) 8.16 (dd, 1H, $J = 7.8, 2.1$ Hz), 8.09 (s, 1H), 7.83 (q, 1H, $J = 7.8$ Hz), 7.72 (s, 1H), 7.25 (s, 1H), 7.09 (s, 1H), 6.77 (dd, 1H, $J = 7.8, 2.1$ Hz), 6.05 (s, 2H), 2.78 (t, 2H, $J = 5.4$ Hz), 1.77 (hex, 2H, $J = 5.4$ Hz), 1.06 (t, 3H, $J = 5.4$ Hz). LC/MS ($M+1$) 362.13.

- I. 6-[2-(6-FLUORO-PYRIDIN-2-YL)-IMIDAZOL-1-YLMETHYL]-8-METHYL-7-PROPYL-IMIDAZO[1,2-B]PYRIDAZINE (122)



- Step 1. Preparation of 2-Acetyl-3-methyl-2-propyl-succinic acid dimethyl ester (119)



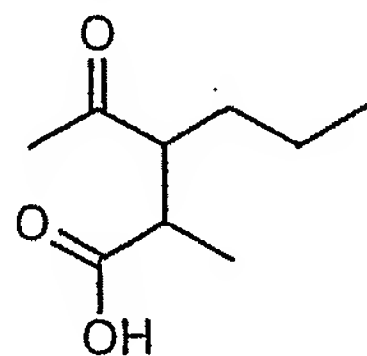
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- To a suspension of NaH (7.58 g, 95% dry, 300 mmol) in DME (200 mL) cooled to 0°C is added dropwise a solution of methyl acetoacetate (34.84 g, 300 mmol) in DME (50 mL). The solution is stirred at room temperature for 45 minutes, Bu_4NI (11.8 g, 30 mmol) is added in one portion followed by slow addition of PrI (56.1 g, 32.2 mL, 330 mmol). The mixture is stirred at room temperature for 15 minutes and then at 75°C overnight. The solvent is removed *in vacuo*, ether (400 mL) is added to the residue and the suspension is stirred vigorously for 20 minutes. The solid is filtered and washed with

ether (3 x 100 ml), and the filtrate is evaporated *in vacuo*. Vacuum distillation of the residue (38-45°C / 1 mmHg) provides methyl 3-propyl acetoacetate as colorless liquid.

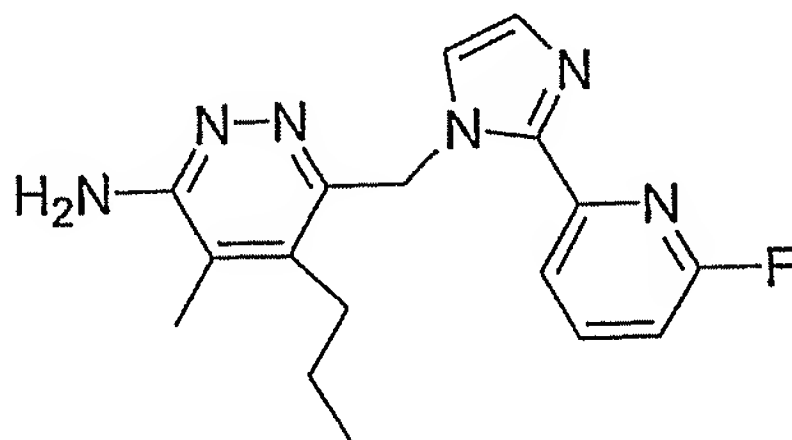
Methyl 3-propyl acetoacetate (7.43 g, 47 mmol) is added dropwise to a suspension of NaH (2.37 g, 95 % dry, 94 mmol) in THF and DMF (3:1, 200 ml), cooled to 0°C. The mixture is stirred at 0°C for 20 minutes and methyl 2-bromo-propionate (10.5 ml, 94 mmol) is added slowly. The mixture is stirred at room temperature for 30 minutes, and then refluxed for 3 hours. The solvent is evaporated *in vacuo* and water (200 ml) is added to the residue. The mixture is extracted with EtOAc (3 x 200 ml) and the combined extracts are washed with brine (250 ml), dried and evaporated. Vacuum distillation of the residue provides the title compound as a clear liquid. (65-70°C / 1 mmHg).

10 Step 2. Preparation of 3-acetyl-2-methyl-hexanoic acid (120)



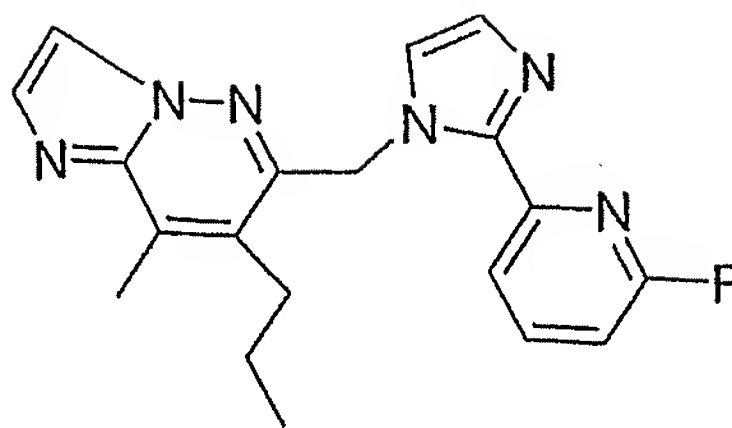
KOH (6.9 g, 123 mmol) is added to a solution of 2-acetyl-3-methyl-2-propyl-succinic acid dimethyl ester (5.0 g, 20.5 mmol) in MeOH (25 ml) and water (25 ml). The mixture is refluxed overnight and excess MeOH is evaporated. The residue is acidified by concentrated HCl to pH = 2 and is refluxed (oil bath 105°C) overnight. The mixture is extracted with EtOAc (4 x 75 ml) and the combined extracts are extracted with 2N aqueous NaOH (4 x 50 ml). The NaOH solution is then cooled to 0°C and acidified with concentrated HCl. The mixture is extracted with EtOAc (4 x 75 ml) and the combined extracts are washed with brine (100 ml), dried (Na₂SO₄) and evaporated *in vacuo*, providing the title compound as a yellow oil.

20 Step 3. Preparation of 6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-methyl-5-propyl-pyridazin-3-ylamine (121)



3-Acetyl-2-methyl-hexanoic acid is converted to 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-methyl-5-propyl-pyridazin-3-ylamine essentially as described in Example 1A (steps 3-11).

25 Step 4. Preparation of 6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-8-methyl-7-propyl-imidazo[1,2-b]pyridazine (122)

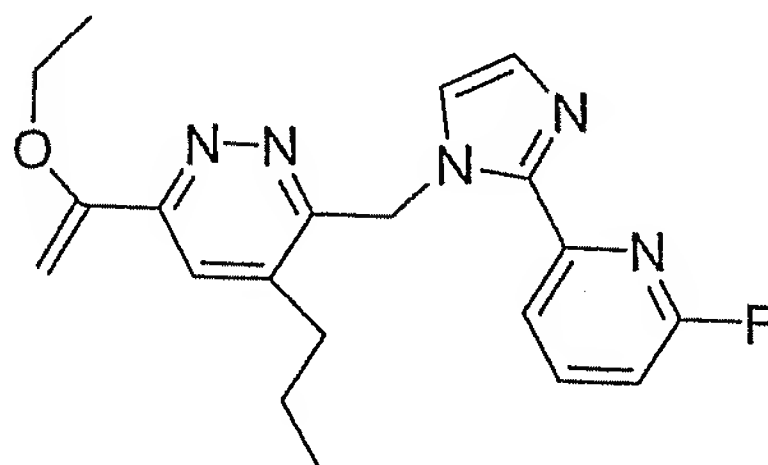


6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-8-methyl-7-propyl-imidazo[1,2-b]pyridazine is prepared as described in Example 1A (step 12). ^1H NMR δ (CDCl_3) 0.92 (t, 3H), 1.45-1.53 (m, 2H), 2.58-2.69 (m, 5H), 6.14 (s, 2H), 6.82 (dd, 1H), 7.03 (d, 1H), 7.18 (d, 1H), 7.61 (d, 1H), 7.73 (d, 1H), 7.83 (q, 1H), 8.16 (dd, 1H).

EXAMPLE 2. SYNTHESIS OF IMIDAZO[1,5-B]PYRIDAZINES

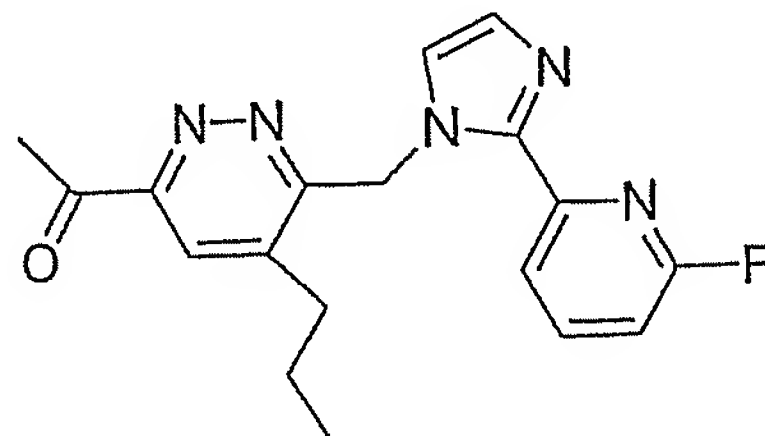
This Example illustrates the synthesis of 2-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-methyl-3-propyl-imidazo[1,5-b]pyridazine (126), a representative imidazo[1,5-b]pyridazine.

Step 1. Preparation of 6-(1-ethoxy-vinyl)-3-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-propyl-pyridazine (123)



To a solution of 6-chloro-3-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-propyl-pyridazine (0.6 g) in toluene (30 mL), tributyltinvinylether (0.98 g) and $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (40 mg) are added. The mixture is degassed for 10 minutes. The mixture is heated at 130°C overnight. The solvent is removed under vacuum to give the crude product which is used in the next step without further purification. LC/MS ($\text{M}+1$) 368.2.

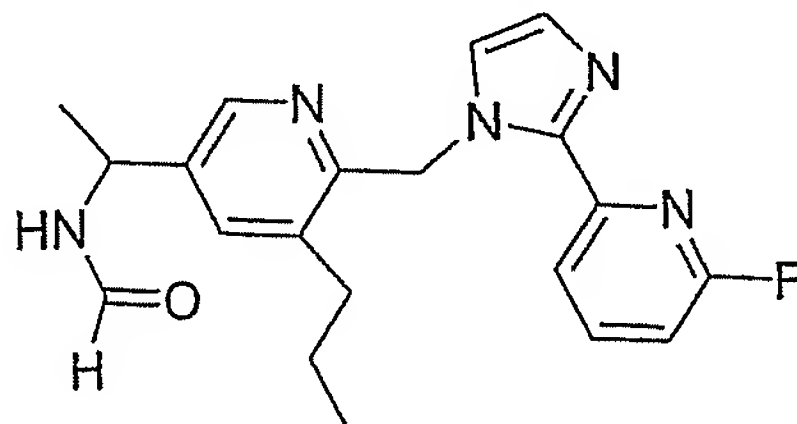
Step 2. Preparation of 1-{6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-yl}-ethanone (124)



The above crude 6-(1-ethoxy-vinyl)-3-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-propyl-pyridazine is dissolved in MeOH (15mL). 6N HCl (20 mL) is added and the mixture is stirred at room temperature for 5 hours. The solvent is removed, neutralized with saturated NaHCO_3 , and extracted with EtOAc. Upon drying, the solvent is evaporated to give the crude product, which is

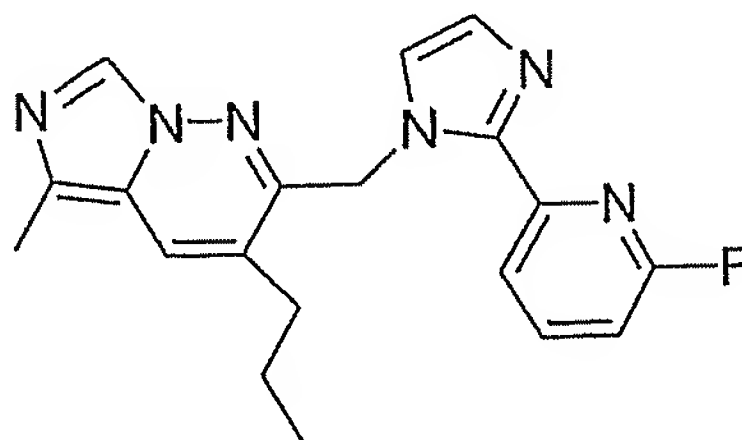
purified by PTLC with EtOAc to give the title compound. ^1H NMR δ (CDCl_3) 8.16 (ddd, 1H, $J = 6, 1.8, 0.6$ Hz), 7.94 (s, 1H), 7.80 (q, 1H, $J = 6$ Hz), 7.21 (d, 1H, $J = 0.6$ Hz), 7.19 (d, 1H, $J = 0.6$ Hz), 6.78 (dd, 1H, $J = 6, 1.8, 0.6$ Hz), 6.25 (s, 2H), 2.80 (m, 5H), 1.63 (hex, 2H, $J = 5.4$ Hz), 0.95 (t, 3H, $J = 5.4$).

Step 3. Preparation of N-(1-{6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-yl}ethyl)formamide (125)



To 0.3g of formamide at 160-180°C is added 1-{6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-yl}-ethanone (0.055g) and formic acid (0.029 g) in 0.5 g of formamide. The mixture is heated at 160-180°C for an additional 1.5 hours. During this period, formic acid (0.029 g) is added. The mixture is cooled to room temperature and poured into water (5mL), and the solution is made alkaline to at least pH 11 with concentrated sodium hydroxide. The solution is extracted with EtOAc, dried over MgSO_4 , evaporated to give a residue. The residue is purified by PTLC with EtOAc to give the title product. ^1H NMR δ (CDCl_3) 8.19 (s, 1H), 8.16 (dd, 1H, $J = 6, 1.8$ Hz), 7.83 (q, 1H, $J = 6$ Hz), 7.83 (q, 1H, $J = 6$ Hz), 7.43 (d, 1H, $J = 0.6$ Hz), 7.19 (d, 1H, $J = 0.6$ Hz), 7.06 (d, 1H, $J = 0.6$ Hz), 6.80 (dd, 1H, $J = 6, 1.8, 0.6$ Hz), 6.21 (dd, 2H, $J = 11.7, 9.0$ Hz), 5.32 (p, 1H, $J = 0.3$ Hz), 2.72 (t, 2H, $J = 5.7$ Hz), 1.63 (Hex, 2H, $J = 5.7$ Hz), 1.54 (d, 3H, $J = 5.1$ Hz), 0.95 (t, 3H, $J = 5.7$ Hz). LC/MS (M+1) 369.2.

Step 4. Preparation of 2-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-methyl-3-propyl-imidazo[1,5-b]pyridazine (126)



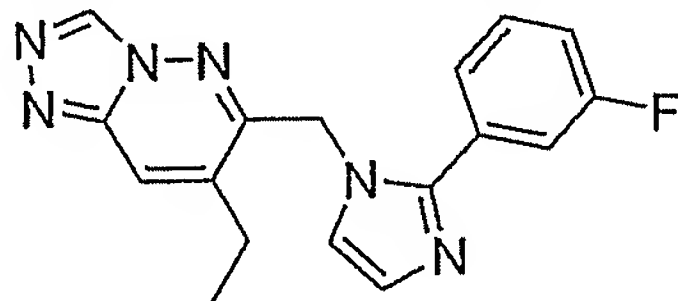
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The mixture of N-(1-{6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyridazin-3-yl}-ethyl)formamide (50 mg) and POCl_3 (2 ml) is heated at reflux for 3 hours. The excess POCl_3 is removed. EtOAc (10 mL) is added, and the solution is washed with saturated NaHCO_3 (5 mL), brine (5 mL), and then dried over MgSO_4 . After evaporation of the solvent, the resulting residue is purified by PTLC with 7% MeOH in DCM to give the title compound. ^1H NMR δ (CDCl_3) 8.16 (ddd, 1H, $J = 6, 1.8, 0.6$ Hz), 8.13 (s, 1H), 7.83 (q, 1H, $J = 6$ Hz), 7.43 (d, 1H, $J = 0.6$ Hz), 7.19 (d, 1H, $J = 0.6$ Hz), 7.06 (d, 1H, $J = 0.6$ Hz), 6.78 (dd, 1H, $J = 6, 1.8, 0.6$ Hz), 5.97 (s, 2H), 2.55 (t, 2H, $J = 5.4$ Hz), 2.44 (s, 3H), 1.63 (hex, 2H, $J = 5.4$ Hz), 0.95 (t, 3H, $J = 5.4$ Hz). LC/MS (M+1) 351.2.

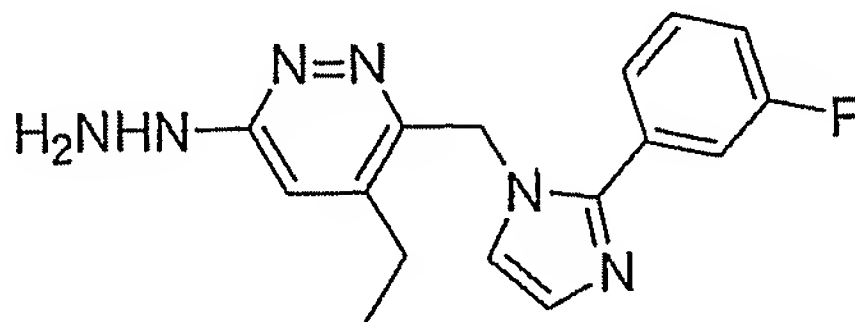
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EXAMPLE 3. SYNTHESIS OF [1,2,4]TRIAZOLO[4,3-B]PYRIDAZINES

A. 7-ETHYL-6-[2-(3-FLUORO-PHENYL)-IMIDAZOL-1-YLMETHYL]-[1,2,4] TRIAZOLO [4,3-B] PYRIDAZINE

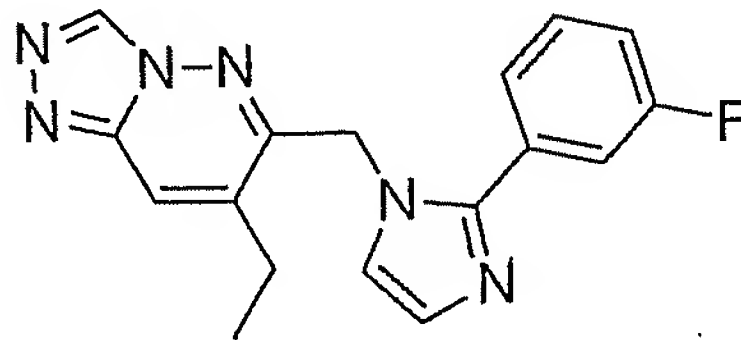


Step 1. Preparation of {5-Ethyl-6-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-pyridazin-3-yl}-hydrazine
5 (127)



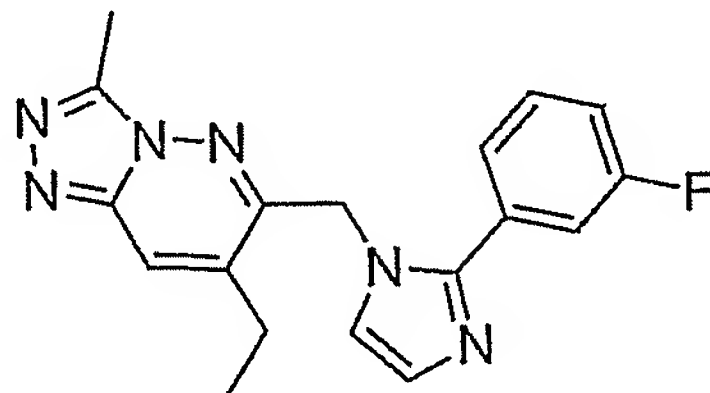
A solution of 6-chloro-4-ethyl-3-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-pyridazine (prepared essentially as described for 6-chloro-3-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-4-propyl-pyridazine in Example 1A, steps 1-9) (712 mg) and hydrazine monohydrate (450 mg, 9 mmol)
10 in EtOH (20 ml) is heated at 120°C in a sealed tube overnight. The solvent is removed *in vacuo* and the yellow solid thus provided is washed with ether (2 x 10 ml), which gives the title compound as a light yellow solid.

Step 2. Preparation of 7-Ethyl-6-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-[1,2,4] triazolo [4,3-b] pyridazine (128)



A solution of {5-ethyl-6-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-pyridazin-3-yl}-hydrazine (38 mg, 0.12 mmol) in formic acid (6 ml) is refluxed for 6 hours. The solvent is removed *in vacuo* and to the residue is added EtOAc (15 ml) and water (15 ml). The layers are separated and the aqueous layer is extracted with EtOAc (3 x 15 ml). The combined extracts are washed with brine (15 ml), dried
20 (Na₂SO₄) and evaporated. PTLC separation of the residue with 5% MeOH in CH₂Cl₂ provides the title compound as a white solid. LC/MS, M+1 323.2; ¹H-NMR (CDCl₃) δ: 9.02 (s, 1H), 7.90 (s, 1H), 7.39-7.46 (m, 1H), 7.25-7.33 (m, 2H), 7.22 (d, 1H), 7.11-7.18 (m, 1H), 6.96 (d, 1H), 5.41 (s, 2H), 2.38 (q, 2H), 1.11 (t, 3H).

B. 7-ETHYL-6-[2-(3-FLUORO-PHENYL)-IMIDAZOL-1-YLMETHYL]-3-METHYL-[1,2,4] TRIAZOLO [4,3-B] PYRIDAZINE (129)



7-Ethyl-6-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-3-methyl-[1,2,4]triazolo[4,3-b]

pyridazine is prepared essentially as described for 7-ethyl-6-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-[1,2,4]triazolo[4,3-b]pyridazine (Example 3A). LC/MS, M+1 337.2; ^1H -NMR (CDCl_3) δ : 7.80 (s, 1H), 7.38-7.45 (m, 1H), 7.30-7.34 (m, 2H), 7.20 (d, 1H), 7.10-7.17 (m, 1H), 6.95 (d, 1H), 5.41 (s, 2H), 2.71 (s, 3H), 2.36 (q, 2H), 1.17 (t, 3H)

10 EXAMPLE 4. LIGAND BINDING ASSAY

A. PURIFIED RAT CORTICAL MEMBRANES

Purified rat cortical membranes are prepared according to Procedure 1 or 2:

Procedure 1: Frozen rat cortex is homogenized in ice cold 50 mM Tris 7.4 (1g cortex/150 ml buffer) using a POLYTRON homogenizer (setting 5 for 30 seconds). The suspension is poured into
15 centrifuge tubes, and then centrifuged for 15 minutes at 20,000 rpm in a SS34 rotor (48,000 x g). The supernatants are discarded and the pellets are washed twice with same buffer and centrifuge speed. The final pellets are stored in covered centrifuge tubes at -80°C . Prior to use, the washed rat cortical membrane is thawed and re-suspended in ice cold 50 mM Tris 7.4 (6.7 mg frozen cortex weight/ml buffer).

20 Procedure 2: Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of Buffer A (0.05 M Tris HCl buffer, pH 7.4 at 4°C). The tissue homogenate is centrifuged in the cold (4°C) at 20,000 x g for 20 minutes. The supernatant is decanted, the pellet rehomogenized in the same volume of buffer, and centrifuged again at 20,000 x g. The supernatant of this centrifugation step is decanted and the pellet stored at -20°C overnight. The pellet is then thawed and resuspended in 25 volumes of
25 Buffer A (original wt/vol), centrifuged at 20,000 x g and the supernatant decanted. This wash step is repeated once. The pellet is finally resuspended in 50 volumes of Buffer A.

B. RADIOLIGAND BINDING ASSAYS

30 The affinity of compounds provided herein for the benzodiazepine site of the GABA_A receptor is confirmed using a binding assay essentially described by Thomas and Tallman (*J. Bio. Chem.* (1981) 156:9838-9842, and *J. Neurosci.* (1983) 3:433-440). Membranes prepared via Procedure 1 are assayed according to Method 1, and membranes prepared via Procedure 2 are assayed according to Method 2.

Method 1: Incubations are carried out at 1.2 mg membrane/well. Duplicate samples containing 180 μ L of membrane suspension, 20 μ L of 3 H-Ro15-1788 (3 H-Flumazenil (PerkinElmer Life Sciences, Boston, MA) and 2 μ L of test compound or control in DMSO (total volume of 202 μ L) are incubated at 4°C for 60 minutes. The incubation is terminated by rapid filtration through untreated 102x258 mm filter mats on Tomtec filtration manifold (Hamden, CT) and the filters are rinsed three times with ice cold 50 mM Tris 7.4. The filters are air dried and counted on a Wallac 1205 Betaplate Liquid Scintillation Counter. Nonspecific binding (control) is determined by displacement of 3 H-RO15-1788 by 10^{-6} M 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-amide. Percent inhibition of total specific binding (Total Specific Binding = Total – Nonspecific) is calculated for each compound.

Method 2: Incubations contain 100 μ l of tissue homogenate, 100 μ l of radioligand (0.5 nM 3 H-RO15-1788, specific activity 80 Ci/mmol) and test compound or control (see below), and are brought to a total volume of 500 μ l with Buffer A. Incubations are carried out for 30 minutes at 4°C and then rapidly filtered through Whatman GFB filters to separate free and bound ligand. Filters are washed twice with fresh Buffer A and counted in a liquid scintillation counter. Nonspecific binding (control) is determined by displacement of 3 H RO15-1788 with 10 μ M Diazepam (Research Biochemicals International, Natick, MA). Data are collected in triplicate, averaged, and percent inhibition of total specific binding (Total Specific Binding = Total – Nonspecific) is calculated for each compound.

Analysis: A competition binding curve is obtained with up to 11 points (e.g., 7 points) spanning the test compound concentration range from 10^{-12} M or 10^{-11} M to 10^{-5} M. IC_{50} and Hill coefficient (“nH”) are determined by fitting the displacement binding data with the aid of SIGMAPLOT software (SPSS Inc., Chicago, IL). The K_i is calculated using the Cheng-Prusoff equation (*Biochemical Pharmacology* 22:3099-3108 (1973)): $K_i = IC_{50} / (1 + [L] / K_d)$, where IC_{50} is determined as by SIGMAPLOT as the concentration of compound which displaces $\frac{1}{2}$ the maximal 3 H-Ro15-1788 binding, [L] is the 3 H-Ro15-1788 concentration used to label the target, and K_d is the binding dissociation constant of 3 H-Ro15-1788, previously determined to be 1.0nM. Preferred compounds of the invention exhibit K_i values of less than 100 nM and more preferred compounds of the invention exhibit K_i values of less than 10 nM.

EXAMPLE 5. ELECTROPHYSIOLOGY

The following assay is used to determine if a compound of the invention alters the electrical properties of a cell and if it acts as an agonist, an antagonist or an inverse agonist at the benzodiazepine site of the GABA_A receptor.

Assays are carried out essentially as described in White and Gurley (NeuroReport 6:1313-1316, 1995) and White, Gurley, Hartnett, Stirling and Gregory (Receptors and Channels 3:1-5, 1995) with modifications. Electrophysiological recordings are carried out using the two electrode voltage-clamp technique at a membrane holding potential of -70 mV. *Xenopus laevis* oocytes are enzymatically

isolated and injected with non-polyadenylated cRNA mixed in a ratio of 4:1:4 for α , β and γ subunits, respectively. Of the nine combinations of α , β and γ subunits described in the White et al. publications, preferred combinations are $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$ and $\alpha_5\beta_3\gamma_2$. Preferably all of the subunit cRNAs in each combination are human clones or all are rat clones. Each of these cloned subunits is described in

5 GENBANK, e.g., human α_1 , GENBANK accession no. X14766, human α_2 , GENBANK accession no. A28100; human α_3 , GENBANK accession no. A28102; human α_5 , GENBANK accession no. A28104; human β_2 , GENBANK accession no. M82919; human β_3 , GENBANK accession no. Z20136; human γ_2 , GENBANK accession no. X15376; rat α_1 , GENBANK accession no. L08490, rat α_2 , GENBANK accession no. L08491; rat α_3 , GENBANK accession no. L08492; rat α_5 , GENBANK accession no.

10 L08494; rat β_2 , GENBANK accession no. X15467; rat β_3 , GENBANK accession no. X15468; and rat γ_2 , GENBANK accession no. L08497. For each subunit combination, sufficient message for each constituent subunit is injected to provide current amplitudes of >10 nA when $1 \mu\text{M}$ GABA is applied.

Compounds are evaluated against a GABA concentration that evokes $<10\%$ of the maximal evocable GABA current (e.g., $1\mu\text{M}$ – $9\mu\text{M}$). Each oocyte is exposed to increasing concentrations of a

15 compound being evaluated (test compound) in order to evaluate a concentration/effect relationship. Test compound efficacy is calculated as a percent-change in current amplitude: $100*((I_c/I)-1)$, where I_c is the GABA evoked current amplitude observed in the presence of test compound and I is the GABA evoked current amplitude observed in the absence of the test compound.

Specificity of a test compound for the benzodiazepine site is determined following completion

20 of a concentration/effect curve. After washing the oocyte sufficiently to remove previously applied test compound, the oocyte is exposed to GABA + $1 \mu\text{M}$ RO15-1788, followed by exposure to GABA + $1 \mu\text{M}$ RO15-1788 + test compound. Percent change due to addition of compound is calculated as described above. Any percent change observed in the presence of RO15-1788 is subtracted from the percent changes in current amplitude observed in the absence of $1 \mu\text{M}$ RO15-1788. These net values

25 are used for the calculation of average efficacy and EC_{50} values by standard methods. To evaluate average efficacy and EC_{50} values, the concentration/effect data are averaged across cells and fit to the logistic equation.

EXAMPLE 6. MDCK TOXICITY ASSAY

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine

30 kidney (MDCK) cell cytotoxicity assay.

$1 \mu\text{L}$ of test compound is added to each well of a clear bottom 96-well plate (PACKARD, Meriden, CT) to give final concentration of compound in the assay of 10 micromolar, 100 micromolar or 200 micromolar. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are

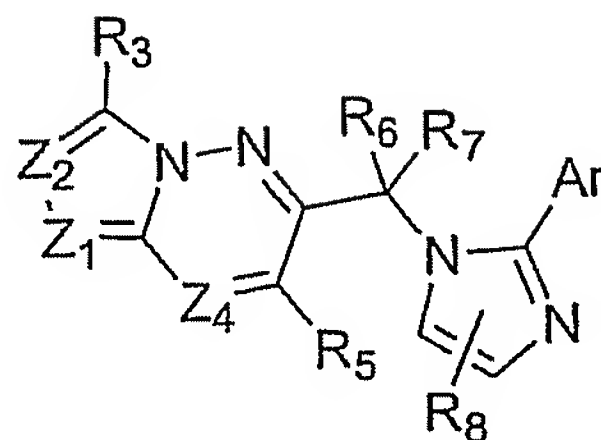
35 maintained in sterile conditions following the instructions in the ATCC production information sheet.

Confluent MDCK cells are trypsinized, harvested and diluted to a concentration of 0.1×10^6 cells/ml with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μL of diluted cells is added to each well, except for five standard curve control wells that contain 100 μL of warm medium without cells. The plate is then incubated at 37°C under 95% O_2 , 5% CO_2 for 2 hours with constant shaking. After incubation, 50 μL of mammalian cell lysis solution is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes.

Compounds causing toxicity will decrease ATP production, relative to untreated cells. The PACKARD, (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit, product no. 6016941, is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 ml of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μL of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM and 12.5 nM. PACKARD substrate solution (50 μL) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 minutes. Luminescence is then measured at 22°C using a luminescence counter (e.g., PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μM of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μM concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

What is claimed is:

1. A compound of the formula:



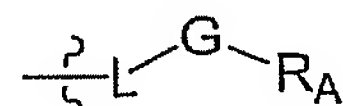
or a pharmaceutically acceptable salt thereof, wherein:

Z₁ is nitrogen or CR₁ and Z₂ is nitrogen or CR₂; such that at least one of Z₁ and Z₂ is nitrogen;

Z₄ is nitrogen or CR₄;

R₁, R₂, R₃ and R₄ are each independently selected from:

- (a) hydrogen, halogen, nitro and cyano; and
- (b) groups of the formula:



wherein:

L is a single covalent bond or C₁-C₈alkylene;

G is a single covalent bond, N(R_B), O, C(=O), C(=O)O, C(=O)N(R_B), N(R_B)C(=O), S(O)_m, CH₂C(=O), S(O)_mN(R_B) or N(R_B)S(O)_m; wherein m is 0, 1 or 2; and

R_A and each R_B are independently selected from:

- (i) hydrogen; and
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 6-membered heterocycloalkyl)C₀-C₄alkyl, (aryl)C₀-C₂alkyl and (heteroaryl)C₀-C₂alkyl, each of which is substituted with from 0 to 4 substituents independently selected from halogen, hydroxy, nitro, cyano, amino, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄alkanoyl, mono- and di(C₁-C₄alkyl)amino, C₁-C₄haloalkyl and C₁-C₄haloalkoxy;

R₅ is hydrogen, halogen, cyano, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₄alkoxy, or mono- or di-(C₁-C₄alkyl)amino, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C₁-C₄alkoxy, C₁-C₂haloalkyl, C₁-C₂haloalkoxy, mono- and di-C₁-C₄alkylamino, C₃-C₈cycloalkyl, phenyl, phenylC₁-C₄alkoxy and 5- or 6-membered heteroaryl;

R₆ and R₇ are independently hydrogen, methyl, ethyl or halogen;

R₈ represents 0, 1 or 2 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C₁-C₄alkyl, C₁-C₄alkoxy, mono- and di(C₁-C₄alkyl)amino, C₃-C₇cycloalkyl, C₁-C₂haloalkyl and C₁-C₂haloalkoxy; and

Ar represents phenyl, naphthyl or a 5- to 10-membered heteroaryl, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C₁-C₈alkyl, C₁-C₈alkenyl, C₁-C₈alkynyl, C₁-C₈alkoxy, (C₃-C₇cycloalkyl)C₀-C₄alkyl, (C₃-C₇cycloalkyl)C₁-C₄alkoxy, C₂-C₈alkyl ether, C₃-C₈alkanone, C₁-C₈alkanoyl, 3- to 7-membered heterocycloalkyl, C₁-C₈haloalkyl, C₁-C₈haloalkoxy, oxo, C₁-C₈hydroxyalkyl, C₁-C₈aminoalkyl, and mono- and di-(C₁-C₈alkyl)aminoC₀-C₈alkyl.

2. A compound or salt according to claim 1, wherein R₈ represents 0 or 1 substituent selected from halogen, C₁-C₂alkyl and C₁-C₂alkoxy.

3. A compound or salt according to claim 1 or claim 2, wherein Ar is substituted with 0, 1, 2 or 3 substituents independently selected from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy, mono- or di-C₁-C₄alkylamino, C₂-C₄alkanoyl, (C₃-C₇cycloalkyl)C₀-C₂alkyl, C₁-C₂haloalkyl and C₁-C₂haloalkoxy.

4. A compound or salt according to claim 1 or claim 2, wherein Ar represents phenyl, pyridyl, thiazolyl, thienyl, pyridazinyl or pyrimidinyl, each of which is substituted with from 0 to 4 substituents.

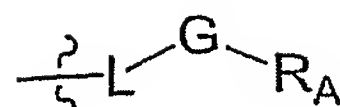
5. A compound or salt according to claim 4, wherein Ar represents phenyl, pyridyl, thiazolyl, thienyl or pyridazinyl, each of which is substituted with from 0 to 3 substituents independently selected from chloro, fluoro, hydroxy, cyano, amino, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₂alkylamino, C₁-C₂haloalkyl and C₁-C₂haloalkoxy.

6. A compound or salt according to claim 5, wherein Ar represents phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl or pyridazin-3-yl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C₁-C₂alkyl, cyano and C₁-C₂alkoxy.

7. A compound or salt according to claim 5, wherein Ar represents 2,6-difluoro-phenyl, 2,5-difluoro-phenyl, 5-fluoro-2-methyl-phenyl, pyridine-2-yl, 3-fluoro-pyridin-2-yl, 3-cyano-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 3-hydroxy-pyridin-2-yl, 3-methoxy-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 6-cyano-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, 6-hydroxy-pyridin-2-yl or 6-methoxy-pyridin-2-yl.

8. A compound or salt according to any one of claims 1-7, wherein R₁, R₂, R₃ and R₄ are independently selected from:

- (a) hydrogen, halogen or cyano; and
- (b) groups of the formula:



wherein:

- (i) L is a single covalent bond;
- (ii) G is a single covalent bond, -NH-, -N(R_B)-, -O-, -C(=O)O- or C(=O)-; and
- (iii) R_A and R_B are independently selected from (1) hydrogen and (2) C₁-C₆alkyl, C₂-C₆alkenyl, (C₃-C₇cycloalkyl)C₀-C₂alkyl, phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl and pyrazinyl, each of which is substituted with from 0 to 4 substituents independently selected from hydroxy, halogen, cyano, amino, C₁-C₂alkyl and C₁-C₂alkoxy.

9. A compound or salt according to claim 8 wherein R₁, R₂, R₃ and R₄ are independently selected from hydrogen, hydroxy, halogen, cyano, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₃-C₇cycloalkyl, C₁-C₄hydroxyalkyl, C₁-C₂haloalkyl, C₁-C₂haloalkoxy, C₁-C₆alkoxycarbonyl, mono- and di-(C₁-C₄alkyl)amino, phenyl and pyridyl.

10. A compound or salt according to claim 9, wherein R₃ and R₄ are independently selected from hydrogen, methyl and ethyl.

11. A compound or salt according to any one of claims 1-10, wherein Z₁ is nitrogen and Z₂ is CR₂.

12. A compound or salt according to claim 11, wherein R₂ is selected from hydrogen, cyano, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₂-C₄alkyl ether, C₃-C₇cycloalkyl, C₁-C₂hydroxyalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl and pyridyl.

13. A compound or salt according to any one of claims 1-10, wherein Z₁ is CR₁ and Z₂ is nitrogen.

14. A compound or salt according to claim 13, wherein R₁ is selected from hydrogen, cyano, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₂-C₄alkyl ether, C₃-C₇cycloalkyl, C₁-C₂hydroxyalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl and pyridyl.

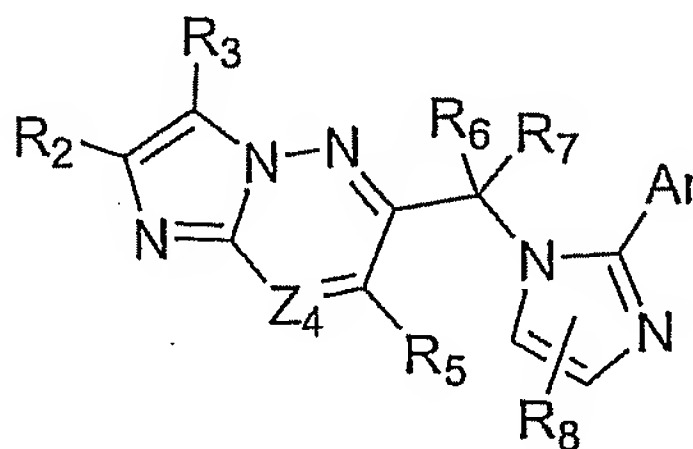
15. A compound or salt according to any one of claims 1-10, wherein Z₁ and Z₂ are nitrogen.

16. A compound or salt according to any one of claims 1-15, wherein R₆ and R₇ are both hydrogen.

17. A compound or salt according to any one of claims 1-16, wherein R_5 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_4 alkoxy, or mono- or di- C_1 - C_4 alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C_1 - C_2 alkoxy, C_3 - C_8 cycloalkyl, phenyl and phenyl C_1 - C_2 alkoxy.

18. A compound or salt according to claim 17, wherein R_5 is ethyl, propyl, butyl, ethoxy or methoxymethyl.

19. A compound or salt according to claim 1, wherein the compound has the formula:



wherein:

R_2 is selected from hydrogen, hydroxy, halogen, cyano, aminocarbonyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkyl, C_2 - C_6 alkyl ether, C_1 - C_4 hydroxyalkyl, C_1 - C_2 haloalkyl, C_1 - C_2 haloalkoxy, C_1 - C_4 alkoxycarbonyl, mono- and di- $(C_1$ - C_4 alkyl)amino, phenyl and pyridyl;

R_3 and R_4 , if present, are independently hydrogen or C_1 - C_4 alkyl;

R_5 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_4 alkoxy, or mono- or di- C_1 - C_4 alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C_1 - C_2 alkoxy, C_3 - C_8 cycloalkyl, phenyl and phenyl C_1 - C_2 alkoxy;

R_6 and R_7 are independently hydrogen, methyl, ethyl or halogen;

R_8 represents 0 or 1 substituent selected from halogen, C_1 - C_2 alkyl and C_1 - C_2 alkoxy; and

Ar represents phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl or 3-pyridazinyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, cyano and C_1 - C_2 alkoxy.

20. A compound or salt according to claim 19, wherein:

R_2 is hydrogen, cyano, aminocarbonyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_2 - C_6 alkyl ether, C_1 - C_4 hydroxyalkyl, C_1 - C_2 haloalkyl or C_1 - C_4 alkoxycarbonyl;

Z_4 is CR_4 ;

R_3 and R_4 are independently hydrogen or C_1 - C_2 alkyl;

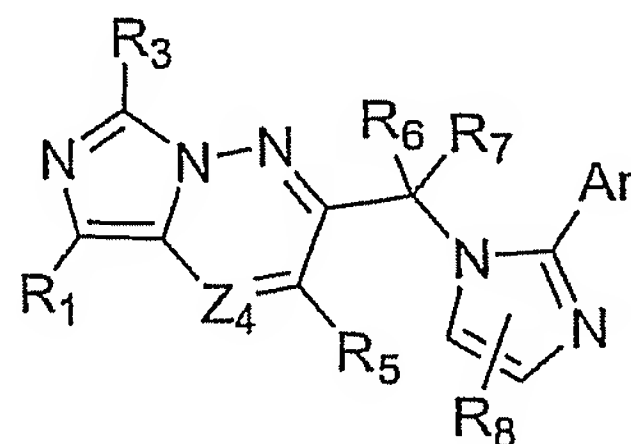
R_5 is C_1 - C_6 alkyl or C_2 - C_6 alkenyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy and C_1 - C_2 alkoxy;

R_6 and R_7 are hydrogen;

R_8 represents 0 substituents; and

Ar represents phenyl or 2-pyridyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

21. A compound or salt according to claim 1, wherein the compound has the formula:



wherein:

R₁ is selected from hydrogen, hydroxy, halogen, cyano, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₇cycloalkyl, C₂-C₆alkyl ether, C₁-C₄hydroxyalkyl, C₁-C₂haloalkyl, C₁-C₂haloalkoxy, C₁-C₄alkoxycarbonyl, mono- and di-(C₁-C₄alkyl)amino, phenyl and pyridyl;

R₃ and R₄, if present, are independently hydrogen or C₁-C₄alkyl;

R₅ is C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₄alkoxy, or mono- or di-C₁-C₄alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C₁-C₂alkoxy, C₃-C₈cycloalkyl, phenyl and phenylC₁-C₂alkoxy;

R₆ and R₇ are independently hydrogen, methyl, ethyl or halogen;

R₈ represents 0 or 1 substituent selected from halogen, C₁-C₂alkyl and C₁-C₂alkoxy; and

Ar represents phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl or 3-pyridazinyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

22. A compound or salt according to claim 21, wherein:

R₁ is hydrogen, cyano, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₂-C₆alkyl ether, C₁-C₄hydroxyalkyl, C₁-C₂haloalkyl or C₁-C₄alkoxycarbonyl;

Z₄ is CR₄;

R₃ and R₄ are independently hydrogen or C₁-C₂alkyl;

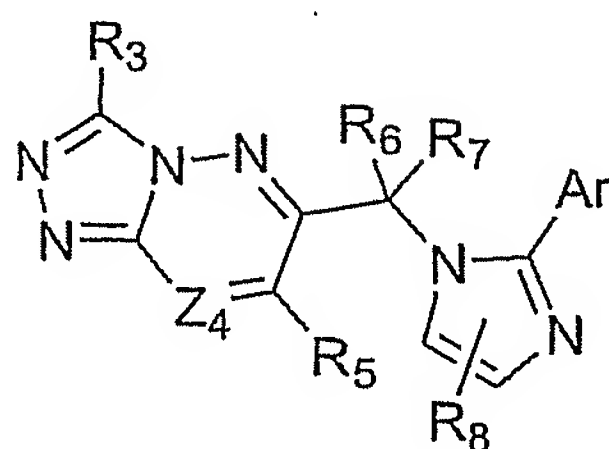
R₅ is C₁-C₆alkyl or C₂-C₆alkenyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy and C₁-C₂alkoxy;

R₆ and R₇ are hydrogen;

R₈ represents 0 substituents; and

Ar represents phenyl or 2-pyridyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

23. A compound or salt according to claim 1, wherein the compound has the formula:



wherein:

R₃ and R₄, if present, are independently hydrogen or C₁-C₄alkyl;

R₅ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₄ alkoxy, or mono- or di-C₁-C₄alkylamino, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, C₁-C₂alkoxy, C₃-C₈cycloalkyl, phenyl and phenylC₁-C₂alkoxy;

R₆ and R₇ are independently hydrogen, methyl, ethyl or halogen;

R₈ represents 0 or 1 substituent selected from halogen, C₁-C₂alkyl and C₁-C₂alkoxy; and

Ar represents phenyl, 2-pyridyl, 1,3-thiazol-2-yl, 2-thienyl or 3-pyridazinyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

24. A compound or salt according to claim 23, wherein:

Z₄ is CR₄;

R₃ and R₄ are independently hydrogen or C₁-C₂alkyl;

R₅ is C₁-C₆alkyl or C₂-C₆alkenyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy and C₁-C₂alkoxy;

R₆ and R₇ are hydrogen;

R₈ represents 0 substituents; and

Ar represents phenyl or 2-pyridyl, each of which is substituted with from 0 to 3 substituents independently selected from fluoro, chloro, C₁-C₂alkyl, C₁-C₂haloalkyl, cyano and C₁-C₂alkoxy.

25. A compound or salt according to any one of claims 1-24, wherein the compound exhibits a K_i of 1 micromolar or less in an assay of GABA_A receptor binding.

26. A compound or salt according to claim 25, wherein the compound exhibits a K_i of 100 nanomolar or less in an assay of GABA_A receptor binding.

27. A compound or salt according to claim 26, wherein the compound exhibits a K_i of 10 nanomolar or less in an assay of GABA_A receptor binding.

28. A pharmaceutical composition comprising a compound or salt according to any one of claims 1-24 in combination with a physiologically acceptable carrier or excipient.

29. A pharmaceutical composition according to claim 28, wherein the pharmaceutical composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

30. A method for the treatment of anxiety, depression, a sleep disorder, attention deficit disorder or Alzheimer's dementia, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or salt according to any one of claims 1-24.

31. A method for potentiating a therapeutic effect of a CNS agent, comprising administering to a patient a CNS agent and a compound or salt according to any one of claims 1-24.

32. A method for improving short term memory in a patient, comprising administering to a patient a therapeutically effective amount of a compound or salt according to any one of claims 1-24.

33. A method for altering the signal-transducing activity of GABA_A receptor, comprising contacting a cell expressing GABA_A receptor with a compound or salt according any one of claims 1-24 in an amount sufficient to detectably alter the electrophysiology of the cell, and thereby altering GABA_A receptor signal-transducing activity.

34. A method according to claim 33, wherein the cell recombinantly expresses a heterologous GABA_A receptor, and wherein the alteration of the electrophysiology of the cell is detected by intracellular recording or patch clamp recording.

35. A method for determining the presence or absence of GABA_A receptor in a sample, comprising the steps of:

- (a) contacting a sample with a compound or salt according claim 1, under conditions that permit binding of the compound to GABA_A receptor;
- (b) removing the compound or salt that is not bound to GABA_A receptor; and
- (c) detecting a level of the compound or salt bound to GABA_A receptor;

and therefrom determining the presence or absence of GABA_A receptor in the sample.

36. A method according to claim 35, wherein the presence or absence of bound compound is detected using autoradiography.

37. A method for determining the presence or absence of GABA_A receptor in a sample, comprising:

determining background binding by, in order:

(a) contacting a first sample with a measured molar concentration of a labeled compound that is known not to bind to GABA_A receptors, under conditions that permit binding of compounds to GABA_A receptors;

(b) washing the first sample under conditions that permit removal of compounds that are not bound to GABA_A receptors; and

(c) detecting as a background binding amount an amount of label remaining after washing;

and

determining GABA_A binding by, in order:

- (d) contacting with a labeled compound or salt according to claim 1 a second sample matched to the first sample, said compound or salt being present at the measured molar concentration of (a) and said contacting being carried out under the conditions used in (a);
- (e) washing the second sample under the conditions used in (b),
- (f) detecting an amount of label remaining in the second sample after washing; and
- (g) subtracting the background binding amount determined in (c) from the amount of label remaining in the second sample determined in (f)

wherein the remainder of a positive amount after the subtraction of (g) indicates the presence of GABA_A receptor in the second sample.

38. A method according to claim 37, wherein the amount of label remaining after washing of the first sample and the second sample is detected using autoradiography.

39. A packaged pharmaceutical preparation comprising a pharmaceutical composition according to claim 28 in a container and instructions for using the composition to treat a patient suffering from anxiety, depression, a sleep disorder, attention deficit disorder, Alzheimer's dementia or short-term memory loss.

40. The use of a compound or salt according to claim 1 for the manufacture of a medicament for the treatment of a condition selected from anxiety, depression, a sleep disorder, an attention deficit disorder, Alzheimer's dementia and short-term memory loss.

41. 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine or a pharmaceutically acceptable salt thereof.

42. 2-tert-butyl-6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine or a pharmaceutically acceptable salt thereof.

43. 2-ethyl-6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine or a pharmaceutically acceptable salt thereof.

44. 2-methyl-6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine or a pharmaceutically acceptable salt thereof.
45. 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-2trifluoromethyl-imidazo[1,2-b]pyridazine or a pharmaceutically acceptable salt thereof.
46. 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine-2-carboxylic acid ethyl ester or a pharmaceutically acceptable salt thereof.
47. 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine-2-carboxylic acid amide or a pharmaceutically acceptable salt thereof.
48. 6-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-7-propyl-imidazo[1,2-b]pyridazine-2-carbonitrile or a pharmaceutically acceptable salt thereof.
49. 6-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-8-methyl-7-propyl-imidazo[1,2-b]pyridazine or a pharmaceutically acceptable salt thereof.
50. 2-[2-(6-fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-5-methyl-3-propyl-imidazo[1,5-b]pyridazine or a pharmaceutically acceptable salt thereof.
51. 7-ethyl-6-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-[1,2,4]triazolo[4,3-b]pyridazine or a pharmaceutically acceptable salt thereof.
52. 7-ethyl-6-[2-(3-fluoro-phenyl)-imidazol-1-ylmethyl]-3-methyl-[1,2,4]triazolo [4,3-b] pyridazine or a pharmaceutically acceptable salt thereof.